

DECLARATION

I, Yoshiaki TODAKA of c/o The Patent Corporate Body ARUGA PATENT OFFICE, 3-6, Nihonbashiningyocho 1-chome, Chuo-ku, Tokyo 103-0013 Japan do solemnly and sincerely declare that I well understand both Japanese and English languages and that I believe the attached English version is a true and complete translation of the Japanese Patent Application No. 10-227449 filed on August 11, 1998 in the name of Daiichi Pharmaceutical Co., Ltd.

July 1, 2005



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No. 10-227449

【Document Name】 APPLICATION FOR PATENT

【Reference Number】 I98081101A

【Filing Date】 August 11, 1998

【Filed to】 Commissioner, Patent Office
Takeshi ISAYAMA

【International Classification】 C07C 15/02, C07C 15/24

【Title of the Invention】 NOVEL SULFONYL DERIVATIVES

【Number of Claims】 17

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【Designation of Fees】

【Number of Advance Payment Register】 005131

【Amount Paid】 21,000 Yen

【List of Appended Documents】

【Document Name】 Specification 1

【Document Name】 Abstract 1

【Request of Identification of Data】 Requested

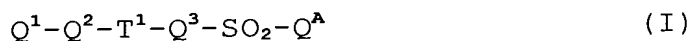
[Document Name] SPECIFICATION

[Title of the Invention] NOVEL SULFONYL DERIVATIVES

[Claims]

[Claim 1] A sulfonyl derivative represented by the following formula (I):

[Chemical formula 1]



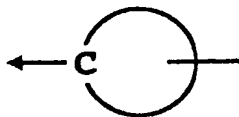
[wherein Q^1 represents a saturated or unsaturated dicyclic fused ring group which may have a substituent or a saturated or unsaturated tricyclic fused ring group which may have a substituent,

Q^2 represents a single bond, an oxygen atom, a sulfur atom, a linear or branched C_{1-6} alkylene group, a linear or branched C_{2-6} alkenylene group, a linear or branched C_{2-6} alkynylene group,

a group $-N(R^1)-CO-$ (in which R^1 represents a hydrogen atom or an alkyl group),

a group $-N(R^2)-(CH_2)_m-$ (in which R^2 represents a hydrogen atom or an alkyl group and m stands for an integer of 0 to 6), or a group of the following formula:

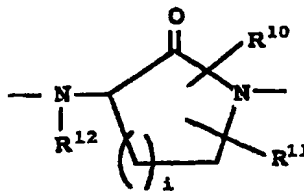
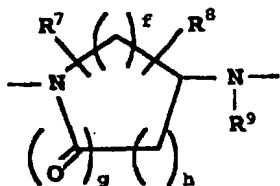
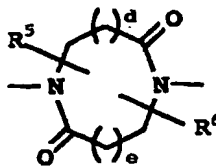
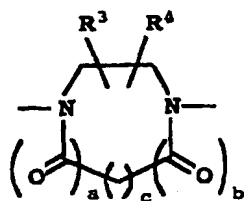
[Chemical formula 2]



(which represents a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent,
 a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, or
 a divalent, saturated or unsaturated dicyclic fused ring group which may have a substituent and $\leftarrow C$ means the bonding of the carbon atom of this group to Q^1),

Q^3 represents any one of the following groups:

[Chemical formula 3]



(in which, when the carbon atom to which each of R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{10} and R^{11} has been bonded is not adjacent to a nitrogen atom, R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{10} and R^{11} each independently represents a hydrogen atom,

a hydroxyl group,

an alkyl group,

an alkoxyl group,
an alkoxyalkyl group,
an alkoxyalkyloxy group,
a hydroxyalkyl group,
a hydroxyalkyloxy group,
a hydroxyalkylcarbonyl group,
a hydroxyalkylsulfonyl group,
a formyl group,
a formylalkyl group,
a formylalkylcarbonyl group,
a formylalkylsulfonyl group,
an alkylcarbonyl group,
an alkylsulfonyl group,
an alkylcarbonylalkyl group,
an alkylsulfonylalkyl group,
a carboxyl group,
a carboxyalkyl group,
a carboxyalkyloxy group,
a carboxyalkylcarbonyl group,
a carboxyalkylsulfonyl group,
a carboxyalkylcarbonylalkyl group,
a carboxyalkylsulfonylalkyl group,
an alkoxycarbonyl group,
an alkoxycarbonylalkyl group,
an alkoxycarbonylalkyloxy group,

an alkoxycarbonylalkylcarbonyl group,
 an alkoxycarbonylalkylsulfonyl group,
 an amino group which may have 1 or 2 substituents,
 an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents or

a group A^1-B^1 - (in which A^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and B^1 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group $-NHCO$ or a group $-NHCO-(C_{1-6} \text{ alkylene})$ group),

when the carbon atom to which each of R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{10} and R^{11} has been bonded is adjacent to a nitrogen

atom, R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{10} and R^{11} each independently represents

- a hydrogen atom,
- an alkyl group,
- a hydroxyalkyl group,
- a hydroxyalkylcarbonyl group,
- a hydroxyalkylsulfonyl group,
- a formyl group,
- a formylalkyl group,
- a formylalkylcarbonyl group,
- a formylalkylsulfonyl group,
- an alkylcarbonyl group,
- an alkylsulfonyl group,
- an alkylcarbonylalkyl group,
- an alkylsulfonylalkyl group,
- a carboxyl group,
- a carboxyalkyl group,
- a carboxyalkylcarbonyl group,
- a carboxyalkylsulfonyl group,
- a carboxyalkylcarbonylalkyl group,
- a carboxyalkylsulfonylalkyl group,
- an alkoxyalkyl group,
- an alkoxy carbonyl group,
- an alkoxy carbonylalkyl group,
- an alkoxy carbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, or

a group A^2-B^2- (in which A^2 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, and B^2 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group $-NHCO$ or a group $-NHCO-(C_{1-6} \text{ alkylene})$ group),

each of R^3 and R^4 , R^5 and R^6 , R^7 and R^8 , and R^{10} and R^{11} may be coupled together with a carbon atom which constitutes the ring and represent a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent,

R^9 and R^{12} each independently represents:

a hydrogen atom,

an alkyl group,

a hydroxyalkyl group,
a hydroxyalkylcarbonyl group,
a hydroxyalkylsulfonyl group,
an alkoxyl group,
an alkoxyalkyl group,
an alkoxyalkylcarbonyl group,
an alkoxyalkylsulfonyl group,
a formyl group,
a formylalkyl group,
a formylalkylcarbonyl group,
a formylalkylsulfonyl group,
an alkylcarbonyl group,
an alkylcarbonylalkyl group,
an alkylsulfonyl group,
an alkylsulfonylalkyl group,
a carboxyalkyl group,
a carboxyalkylcarbonyl group,
a carboxyalkylsulfonyl group,
a carboxyalkylcarbonylalkyl group,
a carboxyalkylsulfonylalkyl group,
an alkoxycarbonyl group,
an alkoxycarbonylalkyl group,
an alkoxycarbonylalkylcarbonyl group,
an alkoxycarbonylalkylsulfonyl group,
an amino group which may have 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxycarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, or

an aminocarbonyloxyalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

R^9 and R^7 or R^8 may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which R^9 has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent,

R^{12} and R^{10} or R^{11} may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which R^{12} has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent,

a, b, d, e and g each independently stands for an integer of 0 or 1, c stands for an integer of 0 to 3, and f,

h and i each independently represents an integer of 1 to 3, with the proviso that the sum of a, b and c stands for an integer of 2 or 3, the sum of d and e stands for an integer of 0 or 1 and the sum of f, g and h stands for an integer of 3 to 5),

Q^A represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent, a saturated or unsaturated tricyclic fused ring group which may have a substituent, a group $Ar-C(H)=N-$ (in which, Ar represents an aryl group which may have a substituent), or a group $Het-C(H)=N-$ (in which, Het represents a heteroaryl group which may have a substituent), and

T^1 represents a carbonyl group,

a group $-CH(R^{13})-$

(in which R^{13} represents a hydrogen atom, an alkyl group, a hydroxyalkyl group having the hydroxyl group which may be protected, an alkoxyalkyl group, a carboxyalkyl group, an alkoxycarbonylalkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent (protecting group)), or

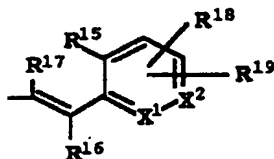
a group $-C(=NOR^{14})-$

(in which R^{14} represents a hydrogen atom, an alkyl group, a carboxyalkyl group, an alkoxycarbonyl group, an aryl group,

an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent)], or salt thereof; or a solvate thereof.

[Claim 2] A sulfonyl derivative according to claim 1, wherein in the formula (I), Q^A represents any one of the below-described groups:

[Chemical formula 4]



[wherein R^{15} represents a hydrogen atom, a hydroxyl group, a nitro group, a cyano group, a halogen atom, an alkyl group, a hydroxyalkyl group, an alkoxyl group, an alkoxyalkyl group, a carboxyl group, a carboxyalkyl group, an alkylcarbonyl group, an alkoxycarbonyl group, an alkoxycarbonylalkyl group, an alkylcarbonyloxy group or a group A^3-B^3 -

(wherein A^3 represents an amino group which may have 1 or 2 substituents, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and B^3 represents a single bond, a carbonyl group, an alkylene group, a carbonyl-

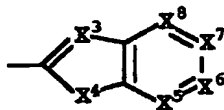
lalkyl group, a carbonylalkyloxy group or an alkylene carbonyloxy group),

R^{16} and R^{17} each independently represents a hydrogen atom, a halogen atom, an alkyl group, a hydroxyalkyl group having a hydroxyl group which may be protected or an alkoxyalkyl group, or R^{16} or R^{17} may be coupled together with R^{15} and represent a C_{1-3} alkylene or alkenylene group,

R^{18} and R^{19} each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxy group, an alkenyl group, an alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a trifluoromethyl group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group, with the proviso that R^{18} and R^{19} do not represent a hydrogen atom at the same time), and

X^1 and X^2 each independently represents a methine group or a nitrogen atom].

[Chemical formula 5]



[wherein X^3 represents a nitrogen atom, or a group $=C(R^{100})-$

(wherein R^{100} represents a hydrogen atom, a halogen atom, an alkyl group, an alkoxy-carbonyl group, an aralkyloxy-carbonylalkyl group, an alkoxy-carbonylalkyl group, a nitro group, an amino group which may have a protecting group or an aminoalkyl group which may have, at the amino moiety thereof, a protecting group),

X^4 represents an oxygen atom, a sulfur atom or a group $-N(R^{101})-$

(wherein R^{101} means a hydrogen atom, an alkyl group, an alkoxy-carbonyl group, an aralkyloxy-carbonyl group, an alkoxy-carbonylalkyl group, an alkylsulfonyl group or an arylsulfonyl group),

X^5 and X^8 each independently represents a nitrogen atom or

a group $-C(R^{102})-$

(wherein R^{102} represents a hydrogen atom or a halogen atom),

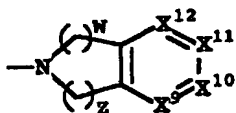
X^6 and X^7 each independently represents a nitrogen atom or

a group $-C(R^{103})-$

(wherein R^{103} represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxy group, an alkenyl group, an alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group,

an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group)].

[Chemical formula 6]



[wherein X^9 and X^{12} each independently represents a nitrogen atom or

a group $-C(R^{104})-$

(wherein R^{104} represents a hydrogen atom or a halogen atom),

X^{10} and X^{11} each independently represents a nitrogen atom or

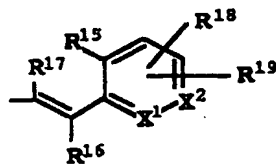
a group $-C(R^{105})-$

(wherein R^{105} represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxy group, an alkenyl group, an alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group, and

w and z each independently represents an integer of 1 or 2], or salt thereof; or a solvate thereof.

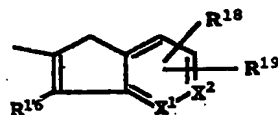
[Claim 3] A sulfonyl derivative according to claim 2, wherein in the formula (I), the group:

[Chemical formula 7]



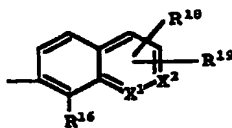
means the following group:

[Chemical formula 8]



or

[Chemical formula 9]

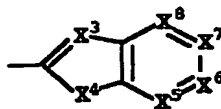


[in the above groups, R^{16} , R^{18} , R^{19} , X^1 and X^2 have the same meanings as defined above], or salt thereof; or a solvate thereof.

[Claim 4] A sulfonyl derivative according to claim 2 or 3, wherein R^{18} represents a halogen atom or an ethynyl group, or salt thereof; or a solvate thereof.

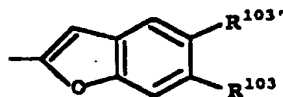
[Claim 5] A sulfonyl derivative according to claim 2, wherein in the formula (I), the group:

[Chemical formula 10]

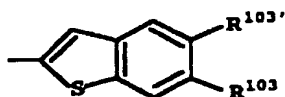


means any one of the following groups:

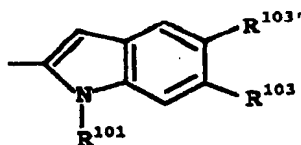
[Chemical formula 11]



[Chemical formula 12]



[Chemical formula 13]

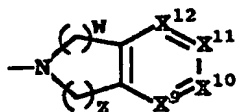


[in the above formulas, R^{101} and R^{103} have the same meanings as defined above and $R^{103'}$ represents similar atoms or groups to R^{103}], or salt thereof; or a solvate thereof.

[Claim 6] A sulfonyl derivative according to claim 5, wherein either one of R^{103} and $R^{103'}$ represents a halogen atom or an ethynyl group, or salt thereof; or a solvate thereof.

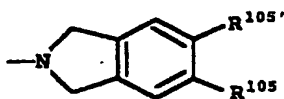
[Claim 7] A sulfonyl derivative according to claim 2, wherein in the formula (I), the group:

[Chemical formula 14]



represents the following group:

[Chemical formula 15]



[wherein R^{105} has the same meaning as defined above and $R^{105'}$ represents similar atoms or groups to R^{105}], or salt thereof; or a solvate thereof.

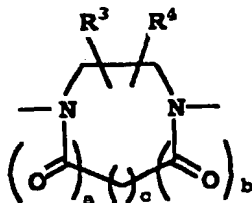
[Claim 8] A sulfonyl derivative according to claim 7, wherein either one of R^{105} or $R^{105'}$ represents a halogen atom or an ethynyl group, or salt thereof; or a solvate thereof.

[Claim 9] A sulfonyl derivative according to any one of claims 1 to 8, wherein Q^1 represent a thienopyridyl group which may have a substituent, tetrahydrothienopyridyl group which may have a substituent, thiazolopyridyl group which may have a substituent or tetrahydrothiazolopyridyl group which may have a substituent, or salt thereof; or a solvate thereof.

[Claim 10] A sulfonyl derivative according to any one of claims 1 to 9, wherein Q^2 represents a single bond, phenylene group, cyclohexylene group or cyclohexenylene group, or salt thereof; or a solvate thereof.

[Claim 11] A sulfonyl derivative according to any one of claims 1 to 10, wherein Q^3 represents the group:

[Chemical formula 16]



[wherein R^3 , R^4 , a , b and c have the same meanings as defined above], or salt thereof; or a solvate thereof.

[Claim 12] A sulfonyl derivative according to any one of claims 1 to , wherein T^1 represents a carbonyl group or a group $-\text{CH}(R^{13})-$ (wherein R^{13} has the same meaning as defined above), or salt thereof; or a solvate thereof.

[Claim 13] A medicament comprising as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 12.

[Claim 14] An inhibitor for an activated coagulation factor X, which comprises as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 12.

[Claim 15] A coagulation suppressor comprising as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 12.

[Claim 16] A preventive and/or remedy for thrombosis or embolism, which comprises as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 12.

[Claim 17] A preventive and/or remedy for cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization, formation of thrombus upon extracorporeal circulation or coagulation upon blood collection, which comprises as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 12.

[Detailed Description of the Invention]

[0001]

[Field of the Invention]

The present invention relates to a novel, orally-administrable sulfonyl derivative or salt thereof which inhibits an activated coagulation factor (which will hereinafter be abbreviated as "FXa"), thereby exhibiting strong anticoagulant action; and a coagulation suppressor or preventive and/or remedy for thrombosis or embolism which comprises the derivative or salt as an effective ingredient.

[0002]

[Prior Art]

Exasperation of coagulation capacity is an important factor for unstable angina, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis,

disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization or formation of thrombus upon extracorporeal circulation. There is accordingly a demand for an excellent anticoagulant which is excellent in dose-responsiveness, has long-lasting effects, has a low risk of hemorrhage, has less side effects and exhibits rapid and sufficient effects even by oral administration (Thrombosis Research, **68**, 507-512, 1992).

[0003]

Studies on anticoagulants based on various acting mechanisms suggest that a FXa inhibitor has a possibility of becoming an excellent anticoagulant. The coagulation system is a series of reactions wherein a large amount of a thrombus is produced through an amplification step due to a multi-stage enzymatic reaction and induces the formation of insoluble fibrin. In the intrinsic system, after the multi-stage reaction following the activation of a contact factor, activated Factor IX activates Factor X on a phospholipid membrane in the presence of activated Factor VIII and a calcium ion, while in the extrinsic system, activated Factor VII activates Factor X in the presence of a tissue factor. In other words, the activation of Factor X into FXa in the coagulation system is an essential reaction in the formation of thrombin. Activated Factor X (FXa) in each system carries out limited proteolysis of prothrombin,

thereby forming thrombin. The resulting thrombin activates the coagulation factors on the upstream side, whereby the formation of thrombin is amplified further. As described above, the coagulation system upstream of FXa is separated into intrinsic and extrinsic systems so that the inhibition of the enzyme of the coagulation system upstream of FXa does not suppress the production of FXa sufficiently, inevitably resulting in the production of thrombin. Furthermore, the coagulation system conducts a self-amplifying reaction so that the suppression of the coagulation system can be accomplished more efficiently by the inhibition of FXa which exists upstream of the thrombin than by the inhibition of the thrombin formed (Thrombosis Research, 15, 617-629(1979)).

[0004]

Another merit of the FXa inhibitor is that an effective dose in a thrombus model is largely different from the dose for extending the bleeding time in an experimental hemorrhage model. From the experimental result, the FXa inhibitor is presumed to be an anticoagulant with a low risk of hemorrhage.

[0005]

As a FXa inhibitor, various compounds are reported. In general, antithrombin III or antithrombin III-dependent penta-saccharide is known to have no inhibitory action against a prothrombinase complex which plays a practical

role in the thrombus formation in vivo (Thrombosis Research, **68**, 507-512(1992); Journal of Clinical Investigation, **71**, 1383-1389(1983); Mebio, August issue, 92-97) and moreover, it does not exhibit effectiveness in oral administration. Although tick anticoagulant peptide (TAP) (Science, **248**, 593-596(1990)) or antistacin (AST) (Journal of Biological Chemistry, **263**, 10162-10167(1988)) isolated from a tick or leech which is a bloodsucker inhibits FXa and exhibits anti-thrombus effects on the models of from venous thrombus to arterial thrombus, it is not effective when orally administered because it is a high-molecular peptide. From such a viewpoint, a low-molecular FXa inhibitor which directly inhibits a coagulation factor without depending on antithrombin III has been developed.

[0006]

[Problems Sought for Solution by the Invention]

An object of the present invention is to provide, as an excellent anticoagulant, a novel sulfonyl derivative or salt thereof, or a solvate thereof which has strong FXa inhibitory action, exhibits prompt, sufficient and long-lasting anti-thrombus effects even by the oral administration and has less side effects.

[0007]

[Means for the Solution of the Problems]

With the forgoing in view, the present inventors have carried out an extensive investigation on the synthesis of

a novel FXa inhibitor and its pharmacological action. As a result, it has been found that a novel sulfonyl derivative or salt thereof, or solvate thereof exhibits strong FXa inhibitory action and strong anticoagulant action, inhibits FXa strongly, promptly and continuously by the oral administration, exhibits anti-coagulant action and anti-thrombus action, is highly safe and is useful as a preventive or remedy for various diseases caused by a thrombus embolus.

[0008]

[Embodiments of the Invention]

The present invention relates to a sulfonyl derivative represented by the below-described formula (I) or salt thereof, or a solvate thereof.

[0009]

Chemical formula (I):

[0010]

[Chemical formula 17]



[wherein, Q^1 represents a saturated or unsaturated dicyclic fused ring group which may have a substituent or a saturated or unsaturated tricyclic fused ring group which may have a substituent.

[0011]

Q^2 represents a single bond, an oxygen atom, a sulfur atom, a linear or branched C_{1-6} alkylene group, a linear or branched C_{2-6} alkenylene group, a linear or branched C_{2-6} al-

kynylene group,

a group $-N(R^1)-CO-$

(in which R^1 represents a hydrogen atom or an alkyl group),

a group $-N(R^2)-(CH_2)_m-$

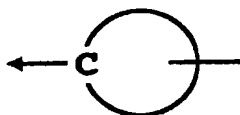
(in which R^2 represents a hydrogen atom or an alkyl group

and m stands for an integer of 0 to 6), or

a group of the following formula:

[0012]

[Chemical formula 18]



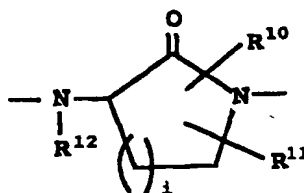
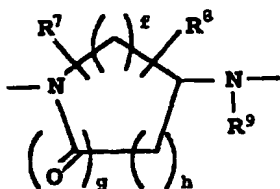
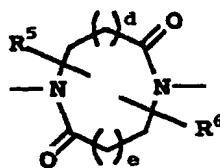
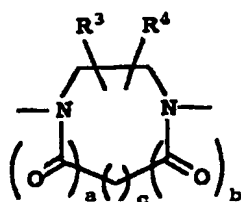
(which represents a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent, a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent or a divalent, saturated or unsaturated dicyclic fused ring group which may have a substituent and $\leftarrow C$ means the bonding of the carbon atom of this group to Q^1).

[0013]

Q^3 represents any one of the following groups.

[0014]

[Chemical formula 19]



(in which when the carbon atom to which each of R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{10} and R^{11} has been bonded is not adjacent to a nitrogen atom, R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{10} and R^{11} each independently represents a hydrogen atom,

- a hydroxyl group,
- an alkyl group,
- an alkoxyl group,
- an alkoxyalkyl group,
- an alkoxyalkyloxy group,
- a hydroxyalkyl group,
- a hydroxyalkyloxy group,
- a hydroxyalkylcarbonyl group,
- a hydroxyalkylsulfonyl group,
- a formyl group,
- a formylalkyl group,
- a formylalkylcarbonyl group,

a formylalkylsulfonyl group,
 an alkylcarbonyl group,
 an alkylsulfonyl group,
 an alkylcarbonylalkyl group,
 an alkylsulfonylalkyl group,
 a carboxyl group,
 a carboxyalkyl group,
 a carboxyalkyloxy group,
 a carboxyalkylcarbonyl group,
 a carboxyalkylsulfonyl group,
 a carboxyalkylcarbonylalkyl group,
 a carboxyalkylsulfonylalkyl group,
 an alkoxycarbonyl group,
 an alkoxycarbonylalkyl group,
 an alkoxycarbonylalkyloxy group,
 an alkoxycarbonylalkylcarbonyl group,
 an alkoxycarbonylalkylsulfonyl group,
 an amino group which may have 1 or 2 substituents,
 an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents or

a group A^1-B^1 - (in which A^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and B^1 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group $-NHCO$ or a group $-NHCO-(C_{1-6} \text{ alkylene})$ group).

[0015]

When the carbon atom to which each of R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{10} and R^{11} has been bonded is adjacent to a nitrogen atom, R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{10} and R^{11} each independently represents

- a hydrogen atom,
- an alkyl group,
- a hydroxyalkyl group,
- a hydroxyalkylcarbonyl group,
- a hydroxyalkylsulfonyl group,
- a formyl group,
- a formylalkyl group,

a formylalkylcarbonyl group,
 a formylalkylsulfonyl group,
 an alkylcarbonyl group,
 an alkylsulfonyl group,
 an alkylcarbonylalkyl group,
 an alkylsulfonylalkyl group,
 a carboxyl group,
 a carboxyalkyl group,
 a carboxyalkylcarbonyl group,
 a carboxyalkylsulfonyl group,
 a carboxyalkylcarbonylalkyl group,
 a carboxyalkylsulfonylalkyl group,
 an alkoxyalkyl group,
 an alkoxycarbonyl group,
 an alkoxycarbonylalkyl group,
 an alkoxycarbonylalkylcarbonyl group,
 an alkoxycarbonylalkylsulfonyl group,
 an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, or
 a group A^2-B^2- (in which A^2 represents a saturated or

unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, and B^2 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group $-NHCO$ or a group $-NHCO-(C_{1-6} \text{ alkylene})$ group).

[0016]

Each of R^3 and R^4 , R^5 and R^6 , R^7 and R^8 , and R^{10} and R^{11} may be coupled together with a carbon atom which constitutes the ring and represent a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent, R^9 and R^{12} each independently represents:

- a hydrogen atom,
- an alkyl group,
- a hydroxyalkyl group,
- a hydroxyalkylcarbonyl group,
- a hydroxyalkylsulfonyl group,
- an alkoxyl group,
- an alkoxyalkyl group,
- an alkoxyalkylcarbonyl group,
- an alkoxyalkylsulfonyl group,
- a formyl group,
- a formylalkyl group,

a formylalkylcarbonyl group,
 a formylalkylsulfonyl group,
 an alkylcarbonyl group,
 an alkylcarbonylalkyl group,
 an alkylsulfonyl group,
 an alkylsulfonylalkyl group,
 a carboxyalkyl group,
 a carboxyalkylcarbonyl group,
 a carboxyalkylsulfonyl group,
 a carboxyalkylcarbonylalkyl group,
 a carboxyalkylsulfonylalkyl group,
 an alkoxycarbonyl group,
 an alkoxycarbonylalkyl group,
 an alkoxycarbonylalkylcarbonyl group,
 an alkoxycarbonylalkylsulfonyl group,
 an amino group which may have 1 or 2 substituents,
 an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents
 an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkyloxycarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents or

an aminocarbonyloxyalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents.

[0017]

R^9 and R^7 or R^8 may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which R^9 has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent.

[0018]

R^{12} and R^{10} or R^{11} may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which R^{12} has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent.

[0019]

a, b, d, e and g each independently stands for an integer of 0 or 1, c stands for an integer of 0 to 3, and f, h and i each independently represents an integer of 1 to 3, with the proviso that the sum of a, b and c stands for an integer of 2 or 3, the sum of d and e stands for an integer of 0 or 1 and the sum of f, g and h stands for an integer of 3 to 5)

Q^A represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a

substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent, a saturated or unsaturated tricyclic fused ring group which may have a substituent, a group Ar-C(H)=N- (in which, Ar represents an aryl group which may have a substituent), or a group Het-C(H)=N- (in which, Het represents a heteroaryl group which may have a substituent).

[0020]

T^1 represents a carbonyl group,

a group $-\text{CH}(\text{R}^{13})-$

(in which R^{13} represents a hydrogen atom, an alkyl group, a hydroxyalkyl group having the hydroxyl group which may be protected, an alkoxyalkyl group, a carboxyalkyl group, an alkoxycarbonylalkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, have a substituent (protecting group)) or

a group $-\text{C}(=\text{NOR}^{14})-$

(in which R^{14} represents a hydrogen atom, an alkyl group, a carboxyalkyl group, an alkoxycarbonyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent.]. A sulfonyl derivative, or salt thereof; or solvate thereof.

[0021]

A description will next be made of the substituents in the sulfonyl group derivative of the formula (I) according to the present invention.

<About group Q^A >

Q^A represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent, a saturated or unsaturated tricyclic fused ring group which may have a substituent, a group $Ar-C(H)=N-$ (in which, Ar represents an aryl group which may have a substituent), or a group $Het-C(H)=N-$ (in which, Het represents a heteroaryl group which may have a substituent).

[0022]

In the group Q^A , the term "arylalkenyl group which may have a substituent" means a group composed of an aryl group and a linear, branched or cyclic C_{2-6} alkenylene group. Examples of the aryl group include phenyl, naphthyl, anthryl and phenanthryl group. Examples of the arylalkenyl group include phenylethenyl group.

[0023]

The "heteroarylalkenyl group which may have a substituent" means a group composed of a heteroaryl group and a linear, branched or cyclic C_{2-6} alkenylene group. The "heteroaryl group" means an aromatic monovalent group having at least one hetero atom and examples include pyridyl,

furyl and thienyl groups. Examples of the heteroarylalkenyl group include pyridylethenyl group.

[0024]

The "saturated or unsaturated, dicyclic or tricyclic fused ring group which may have a substituent" means: 1) a group obtained by the condensation of saturated or unsaturated 5- or 6-membered cyclic hydrocarbon groups which may have a substituent, 2) a group obtained by the condensation of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and 3) a group obtained by the condensation of saturated or unsaturated 5- or 6-membered heterocyclic groups which may have a substituent.

[0025]

Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl groups. When the group has, similar to a cyclopentenyl group, plural structural isomers, they are all embraced in it.

[0026]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or

6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl and triazinyl. Where the group has plural structural isomers as the pyranyl, it is to be noted that they are all embraced in it.

[0027]

Examples of the group 1) include indenyl, indanyl, naphthyl, tetrahydronaphthyl, anthryl and phenanthryl; those of the group 2) include benzofuranyl, benzothienyl, indolyl, indolinyl, quinolyl, benzodiazinyl and tetrahydroisoquinolyl; and those of the group 3) include naphthyridinyl, tetrahydrothienopyridyl, tetrahydrothiazolopyridyl and tetrahydropyridinopyridyl.

[0028]

The aryl group in the group Ar-C(H)=N- (wherein Ar represents an aryl group which may have a substituent) means an aryl group similar to that described above. The group Ar-C(CH)=N- means a group composed of a phenyl group which may have a substituent and a group -C(H)=N- or the like.

[0029]

The heteroaryl group in the group Het-C(H)=N- (wherein Het represents a heteroaryl group which may have a substituent) means a heteroaryl group similar to that described above. The group Het-C(H)=N- means a group composed of a pyridyl group which may have a substituent and a group Het-C(H)=N- .

[0030]

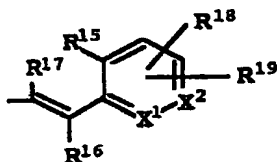
Each of the arylalkenyl group, heteroarylalkenyl group, saturated or unsaturated dicyclic fused ring group, saturated or unsaturated tricyclic fused ring group, the group Ar-C(H)=N- and the group Het-C(H)=N- may have 1 or 2 substituents. Examples of the substituent include a hydroxyl group, halogen atoms such as fluorine, chlorine, bromine and iodine, halogenomethyl groups having 1 to 3 halogen atoms substituted, an amino group, a cyano group, an aminomethyl group, an amidino group, a hydroxyamidino group, linear, branched or cyclic C_{1-6} alkyl groups (ex. methyl and ethyl), linear, branched or cyclic C_{1-6} alkoxy groups (ex. methoxyl and ethoxyl), linear, branched or cyclic C_{2-7} alkoxy-carbonylamidino groups (ex. methoxycarbonylamidino and ethoxycarbonylamidino), linear, branched or cyclic C_{2-6} alkenyl groups (ex. vinyl and allyl), linear, branched or cyclic C_{2-6} alkynyl groups (ex. ethynyl and propynyl), linear, branched or cyclic C_{2-6} alkoxy-carbonyl groups (ex. methoxycarbonyl and ethoxycarbonyl) and amino-carbonyl groups.

[0031]

More specifically, the group Q^A represents any one of the following groups.

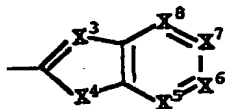
[0032]

[Chemical formula 20]



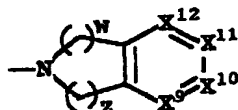
[0033]

[Chemical formula 21]



[0034]

[Chemical formula 22]



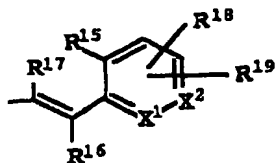
[0035]

A description will next be made of the substituent in these groups.

In the group

[0036]

[Chemical formula 23]



R^{15} represents a hydrogen atom, a hydroxyl group, a nitro group, a cyano group, a halogen atom, an alkyl group, a hydroxyalkyl group, an alkoxyl group, an alkoxyalkyl group, a carboxyl group, a carboxyalkyl group, an alkylcarbonyl group, an alkoxycarbonyl group, an alkoxycarbonylalkyl group, an alkylcarbonyloxy group or a group A^3-B^3

(wherein, A^3 represents an amino group which may have 1 or 2 substituents, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and B^3 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylencarbonyloxy group).

[0037]

In R^{15} , examples of the halogen atom include fluorine, chlorine, bromine and iodine.

[0038]

Examples of the alkyl group include linear, branched or cyclic C_{1-6} alkyl groups such as methyl, ethyl, isopropyl and cyclopropyl.

[0039]

The "hydroxyalkyl group" means a group composed of a hydroxyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples of the alkylene group include methylene, ethylene, trimethylene, propylene and cyclohexylene. Examples of the hydroxyalkyl group include hydroxymethyl and hydroxyethyl.

[0040]

The "alkoxyl group" means a group formed of a linear, branched or cyclic C₁₋₆ alkyl group and an oxygen atom. Examples include methoxyl, ethoxyl and isopropoxyl.

[0041]

The "alkoxyalkyl group" means a group formed of a linear, branched or cyclic C₁₋₆ alkoxyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include methoxymethyl, methoxyethyl and ethoxymethyl.

[0042]

The "carboxyalkyl group" means a group formed of a carboxyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include carboxymethyl and carboxyethyl.

[0043]

The "alkylcarbonyl group" means a group formed of a linear, branched or cyclic C₁₋₆ alkyl group and a carbonyl group. Examples include methylcarbonyl and ethylcarbonyl.

[0044]

The "alkoxycarbonyl group" means a group formed of a linear, branched or cyclic alkoxyl group and a carbonyl group. Examples include methoxycarbonyl and ethoxycarbonyl.

[0045]

The "alkoxycarbonylalkyl group" means a group formed of a linear, branched or cyclic C₂₋₇ alkoxycarbonyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include methoxycarbonylethyl and ethoxycarbonylmethyl.

[0046]

The "alkylcarbonyloxy group" means a group formed of a linear, branched or cyclic C₂₋₇ alkylcarbonyl group and an oxygen atom. Examples include methylcarbonyloxy, ethylcarbonyloxy and isopropylcarbonyloxy.

[0047]

In the group A³-B³-, A³ means an amino group which may have 1 or 2 substituents, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent.

[0048]

When A³ means an amino group which may have 1 or 2 substituents, B³ represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylencarbonyloxy group. The group

A³-B³- therefore means, for example, a group as shown in the following class (A).

[0049]

Class (A):

- an amino group which may have 1 or 2 substituents,
- an aminocarbonyl group which may have, at the amino moiety thereof, may have 1 or 2 substituents,
- an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
- an aminocarbonylalkyl group which may have, at the amino moiety thereof, may have 1 or 2 substituents,
- an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,
- an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents and
- an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents.

[0050]

A description will next be made of the groups shown in Class (A).

[0051]

The "aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of an amino group which may have 1 or 2 substituents and a carbonyl group.

[0052]

The "aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of an amino group which may have 1 or 2 substituents and a linear, branched or cyclic C₁₋₆ alkylene group. Examples of the aminoalkyl group include aminomethyl and aminoethyl.

[0053]

The "aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of the above-described aminocarbonyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples of the aminocarbonylalkyl group include aminocarbonylmethyl and aminocarbonylethyl.

[0054]

The "aminocarbonylalkyloxy group which may have, at the amino moiety, 1 or 2 substituents" means a group formed of the above-described aminocarbonylalkyl group which may have a substituent and an oxygen atom. Examples of the aminocarbonylalkyloxy group include aminocarbonylmethoxyl and aminocarbonylethoxyl.

[0055]

The "aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of the above-described aminoalkyl group which may have a substituent and a carbonyl group. Examples of the aminoalkylcarbonyl group include aminomethylcarbonyl and

aminoethylcarbonyl.

[0056]

The "aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of the above-described aminoalkylcarbonyl group which may have a substituent and an oxygen atom. Examples of the aminoalkylcarbonyloxy group include aminomethylcarbonyloxy and aminoethylcarbonyloxy.

[0057]

Examples of the substituent which can be substituted for an amino group (moiety) include those as shown in the following Class (1).

[0058]

Class (1):

- an alkyl group,
- an alkenyl group,
- a halogenoalkyl group,
- a halogenoalkenyl group,
- a hydroxyalkyl group,
- a hydroxyalkylcarbonyl group,
- a hydroxyalkylsulfonyl group,
- an alkoxyl group,
- an alkoxyalkyl group,
- an alkoxyalkylcarbonyl group,
- an alkoxyalkylsulfonyl group,

a formyl group,
 a formylalkyl group,
 a formylalkylcarbonyl group,
 a formylalkylsulfonyl group,
 an alkylcarbonyl group,
 an alkylcarbonylalkyl group,
 an alkylsulfonyl group,
 an alkylsulfonylalkyl group,
 a carboxyalkyl group,
 a carboxyalkylcarbonyl group,
 a carboxyalkylsulfonyl group,
 a carboxyalkylcarbonylalkyl group,
 a carboxyalkylsulfonylalkyl group,
 an alkoxycarbonyl group,
 an alkoxycarbonylalkyl group,
 an alkoxycarbonylalkylcarbonyl group,
 an alkoxycarbonylalkylsulfonyl group,
 a trifluoromethylsulfonyloxyalkenyl group and
 a group a^3-b^3-

(wherein a^3 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or saturated or unsaturated 5- or 6-membered heterocyclic group which may have one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, an alkoxyl group, an alkyl group, a cyano group, a nitro group, a carboxyl group, an alkoxycarbonyl group and an

aminocarbonyl group.

b³ represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group, an alkylenecarbonyloxy group, an alkyleneaminocarbonyl group, an alkyleneaminocarbonylalkyl group, an alkyleneaminosulfonyl group or an alkyleneaminosulfonylalkyl group.

[0059]

The substituents which can be substituted for an amino group (moiety) in Class (1) will next be described.

[0060]

The "alkyl group" means a linear, branched or cyclic C₁₋₆ alkyl group.

[0061]

The "alkenyl group" means a linear, branched or cyclic C₂₋₆ alkenyl group. Examples include vinyl and allyl.

[0062]

The "halogenoalkyl group" means a group formed of a halogen atom and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include chloromethyl and bromoethyl.

[0063]

The "halogenoalkenyl group" means a group formed of a halogen atom and a linear or branched C₂₋₆ alkenylene group. Examples include chlorovinyl and bromoallyl groups. There is no particular limitation on the position of a double bond.

[0064]

The "hydroxyalkyl group" means a group formed of a hydroxyl group and a linear, branched or cyclic C₂₋₆ alkylene group. Examples include hydroxyethyl and hydroxypropyl.

[0065]

The "hydroxyalkylcarbonyl group" means a group formed of the above-described hydroxyalkyl group and a carbonyl group. Examples include hydroxymethylcarbonyl and hydroxyethylcarbonyl.

[0066]

The "hydroxyalkylsulfonyl group" means a group formed of the above-described hydroxyalkyl group and a sulfonyl group. Examples include hydroxymethylsulfonyl and hydroxyethylsulfonyl.

[0067]

The "alkoxyl group" means a linear, branched or cyclic C₁₋₆ alkoxyl group.

[0068]

The "alkoxyalkyl group" means a group formed of a linear, branched or cyclic C₁₋₆ alkoxyl group and a linear, branched or cyclic C₂₋₆ alkylene group. Examples include methoxyethyl, ethoxyethyl and methoxypropyl.

[0069]

The "alkoxyalkylcarbonyl group" means a group formed of the above-described alkoxyalkyl group and a carbonyl group. Examples include methoxyethylcarbonyl and ethoxy-

methylcarbonyl.

[0070]

The "alkoxyalkylsulfonyl group" means a group formed of the above-described alkoxyalkyl group and a sulfonyl group. Examples include methoxyethylsulfonyl and ethoxymethylsulfonyl.

[0071]

The "formylalkyl group" means a group formed of a formyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include formylmethyl and formylethyl.

[0072]

The "formylalkylcarbonyl group" means a group formed of the above-described formylalkyl group and a carbonyl group. Examples include formylmethylcarbonyl and formylethylcarbonyl.

[0073]

The "formylalkylsulfonyl group" means a group formed of the above-described formylalkyl group and a sulfonyl group. Examples include formylmethylsulfonyl and formylethylsulfonyl.

[0074]

The "alkylcarbonyl group" means a group formed of a linear, branched or cyclic C₁₋₆ alkyl group and a carbonyl group. Examples include methylcarbonyl and ethylcarbonyl.

[0075]

The "alkylcarbonylalkyl group" means a group formed of

the above-described alkylcarbonyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include methylcarbonylmethyl and ethylcarbonylmethyl.

[0076]

The "alkylsulfonyl group" means a group formed of the above-described alkyl group and a sulfonyl group. Examples include methylsulfonyl and ethylsulfonyl.

[0077]

The "alkylsulfonylalkyl group" means a group formed of the above-described alkylsulfonyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include methylsulfonylmethyl and ethylsulfonylmethyl.

[0078]

The "carboxyalkyl group" means a group composed of a carboxyl group and a linear, branched or cyclic C₁₋₆ alkylene group.

[0079]

The "carboxyalkylcarbonyl group" means a group formed of the above-described carboxyalkyl group and a carbonyl group. Examples include carboxymethylcarbonyl and carboxyethylcarbonyl.

[0080]

The "carboxyalkylsulfonyl group" means a group formed of the above-described carboxyalkyl group and a sulfonyl group. Examples include carboxymethylsulfonyl and carboxyethylsulfonyl.

[0081]

The "carboxyalkylcarbonylalkyl group" means a group formed of the above-described carboxyalkylcarbonyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include carboxymethylcarbonylmethyl and carboxyethylcarbonylmethyl.

[0082]

The "carboxyalkylsulfonylalkyl group" means a group formed of the above-described carboxyalkylsulfonyl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include carboxymethylsulfonylmethyl and carboxyethylsulfonylmethyl.

[0083]

The "alkoxycarbonyl group" means a group formed of a linear, branched or cyclic C₁₋₆ alkoxy and a carbonyl group.

[0084]

The "alkoxycarbonylalkyl group" means a group formed of the above-described alkoxycarbonyl group and a linear, branched or cyclic C₁₋₆ alkylene group.

[0085]

The "alkoxycarbonylalkylcarbonyl group" means a group formed of the above-described alkoxycarbonylalkyl group and a carbonyl group. Examples include methoxycarbonylethylcarbonyl and ethoxycarbonylmethylcarbonyl.

[0086]

The "alkoxycarbonylalkylsulfonyl group" means a group of the above-described alkoxycarbonylalkyl group and a sulfonyl group. Examples include methoxycarbonylethylsulfonyl and ethoxycarbonylmethylsulfonyl.

[0087]

The "trifluoromethylsulfonyloxyalkenyl group" means a group formed of a trifluoromethylsulfonyloxy group and a linear or branched C₂₋₆ alkenylene group. Examples include trifluoromethylsulfonyloxyvinyl and trifluoromethylsulfonyloxyallyl.

[0088]

In the group a³-b³-, a³ represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent such as a halogen atom. Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. Where the group has, as the cyclopentenyl, plural structural isomers, they are all embraced in it.

[0089]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen

and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl and triazinyl. Where the group has, as the pyranyl, plural structural isomers, they are all embraced in it.

[0090]

b^3 represents a single bond or a divalent group such as carbonyl, alkylene, carbonylalkyl, carbonylalkyloxy, alkylencarbonyloxy, alkyleneaminocarbonyl, alkyleneaminocarbonylalkyl, alkyleneaminosulfonyl or alkyleneaminosulfonylalkyl. The "alkylene group" means a linear, branched or cyclic C_{1-6} alkylene group.

[0091]

The "carbonylalkyl group" means a group formed of a carbonyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include carbonylmethyl and carbonylethyl.

[0092]

The "carbonylalkyloxy group" means a group formed of the above-described carbonylalkyl group and an oxygen atom. Examples include carbonylmethoxy and carbonylethoxy.

[0093]

The "alkylenecarbonyloxy group" means a group formed of a linear, branched or cyclic C₁₋₆ alkylene group, a carbonyl group and an oxygen atom. Examples include methylenecarbonyloxy and ethylenecarbonyloxy.

[0094]

The "alkyleneaminocarbonyl group" means a group formed of a linear, branched or cyclic C₁₋₆ alkylene group, an imino group and a carbonyl group. Examples include methyleneaminocarbonyl and ethyleneaminocarbonyl.

[0095]

The "alkyleneaminocarbonylalkyl group" means a group formed of the above-described alkyleneaminocarbonyl and a linear, branched or cyclic C₁₋₆ alkylene. Examples include methyleneaminocarbonylmethyl and ethyleneaminocarbonylmethyl.

[0096]

The "alkyleneaminosulfonyl group" means a group formed of a linear, branched or cyclic C₁₋₆ alkylene group, an imino group and a sulfonyl group. Examples include methyleneaminosulfonyl and ethyleneaminosulfonyl.

[0097]

The "alkyleneaminosulfonylalkyl group" means a group formed of the above-described alkyleneaminosulfonyl and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include methyleneaminosulfonylmethyl and ethyleneaminosul-

fonylmethyl.

[0098]

A description will next be made of the substituents which can be introduced into a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group as the above-described a^3 . Examples include halogen atoms, an alkoxyl group, an alkyl group, an alkoxycarbonyl and an aminocarbonyl group.

[0099]

As the group a^3-b^3 -, there exist various kinds according to the combination of a^3 and b^3 . Examples include:

a saturated or unsaturated, 5- or 6-membered cyclic hydrocarbon group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and a carbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and a carbonylalkyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a carbonylalkyloxy group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkylencarbonyloxy group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkyleneaminocarbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkyleneaminocarbonylalkyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkyleneaminosulfonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkyleneaminosulfonylalkyl group, and the like.

[0100]

In addition to the above-described Class (1), the following Class (2) can be given as examples of the substituent which can be substituted for the amino group (moiety).

[0101]

Class (2):

an amino group which may have 1 or 2 substituents selected from the above-described Class (1),

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminocarbonylalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminocarbonylalkylsulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminosulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminosulfonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminoalkylsulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminosulfonylalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected the

above-described from Class (1) and

an aminosulfonylalkylsulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected the above-described from Class (1).

[0102]

A description will next be made of the substituents of Class (2).

[0103]

The aminoalkyl, aminocarbonyl, aminocarbonylalkyl and aminoalkylcarbonyl groups in Class (2) have the same meanings as described above.

[0104]

The "aminoalkyl group which may have a substituent at the amino moiety" means a group formed of the above-described amino group which may have a substituent and a linear, branched or cyclic C₂₋₆ alkylene group. Examples of the aminoalkyl group include aminoethyl and aminopropyl.

[0105]

The "aminocarbonylalkylcarbonyl group which may have a substituent at the amino moiety" means a group formed of the above-described aminocarbonylalkyl group which may have a substituent and a carbonyl group. Examples of the aminocarbonylalkylcarbonyl group include aminocarbonylmethylcarbonyl and aminocarbonylethylcarbonyl.

[0106]

The "aminocarbonylalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described aminocarbonylalkyl group which may have a substituent and a sulfonyl group. Examples of the aminocarbonylalkylsulfonyl group include aminocarbonylmethylsulfonyl and aminocarbonylethylsulfonyl.

[0107]

The "aminosulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described amino group which may have a substituent and a sulfonyl group.

[0108]

The "aminosulfonylalkyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described aminosulfonyl group which may have a substituent and a linear, branched or cyclic C₁₋₆ alkylene group. Examples of the aminosulfonylalkyl group include aminosulfonylmethyl and aminosulfonylethyl.

[0109]

The "aminoalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of an aminoalkyl group which may have the above-described substituent and a sulfonyl group. Examples of the aminoalkylsulfonyl group include aminomethylsulfonyl and aminoethylsulfonyl.

[0110]

The "aminosulfonylalkylcarbonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described aminosulfonylalkyl group which may have a substituent and a carbonyl group. Examples of the aminosulfonylalkylcarbonyl group include aminosulfonylmethylcarbonyl and aminosulfonylethylcarbonyl.

[0111]

The "aminosulfonylalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described aminosulfonylalkyl group which may have a substituent and a sulfonyl group. Examples of the aminosulfonylalkylsulfonyl group include aminosulfonylmethylsulfonyl and aminosulfonylethylsulfonyl.

[0112]

A³ also represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent. Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl groups. Where the group has plural structural isomers as the cyclopentenyl group, they are all embraced in it.

[0113]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero

atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has plural structural isomers as pyranyl, they are all embraced in it.

[0114]

When A^3 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, B^3 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylencarbonyloxy group. Accordingly, the group A^3-B^3- , for example, represents a group as shown in the following Class (B):

[0115]

Class (B):

a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and a carbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group, an alkylene group and an oxygen atom,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group and a carbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group, a carbonyl group and an oxygen atom, and the like.

[0116]

A description will next be made of the groups shown in Class (B).

[0117]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and a carbonyl group,

examples of the group formed of the cyclic hydrocarbon group and a carbonyl group include cyclopentylcarbonyl and phenylcarbonyl; while those of the group formed of the heterocyclic group and a carbonyl group include furylcarbonyl, thienylcarbonyl and pyridylcarbonyl groups.

[0118]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and an alkylene group, the "group formed of a cyclic hydrocarbon group and an alkylene group" means a group formed of the above-described cyclic hydrocarbon group and a linear, branched or cyclic C₁₋₆ alkylene group, for example, cyclohexylmethyl and benzyl, while the "group formed of a heterocyclic group and an alkylene group" means a group formed of the above-described heterocyclic group and a linear, branched or cyclic C₁₋₆ alkylene group, for example, furylmethyl, thienylethyl and pyridylpropyl.

[0119]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group and an alkylene group, the "group formed of a cyclic hydrocarbon group, a carbonyl group and an alkylene group" means a group formed of the above-described cyclic hydrocarbon group, a carbonyl group and a linear, branched or cyclic

C₁₋₆ alkylene group, for example, cyclopentadienylcarbonylmethyl and phenylcarbonylethyl, while the "group formed of a heterocyclic group, a carbonyl group and an alkylene group" means a group formed of the above-described heterocyclic group, a carbonyl group and a linear, branched or cyclic C₁₋₆ alkylene group, for example, furylcarbonylmethyl, thienylcarbonylethyl and pyridylcarbonylpropyl.

[0120]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group, an alkylene group and an oxygen atom, the "group formed of a cyclic hydrocarbon group, a carbonyl group, an alkylene group and an oxygen atom" means a group composed of the above-described group, which is composed of a cyclic hydrocarbon group, a carbonyl group and an alkylene group, and an oxygen atom, for example, cyclopentylcarbonylmethoxy and phenylcarbonylethoxy, while the "group formed of a heterocyclic group, a carbonyl group, an alkylene group and an oxygen atom" means a group composed of the above-described group, which is composed of a heterocyclic group, a carbonyl group and an alkylene group, and an oxygen atom, for example, furylcarbonylmethoxy, thienylcarbonylethoxy and pyridylcarbonylpropoxy.

[0121]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group and a carbonyl group, "the group formed of a cyclic hydrocarbon group, an alkylene group and a carbonyl group" means a group composed of the above-described group, which is formed of a cyclic hydrocarbon group and an alkylene group, and a carbonyl group, for example, cyclohexylmethylcarbonyl and phenylethylcarbonyl, while "the group formed of a heterocyclic group, an alkylene group and a carbonyl group" means a group composed of the above-described group, which is formed of a heterocyclic group and an alkylene group, and a carbonyl group, for example, furylmethylcarbonyl, thienylethylcarbonyl and pyridylpropylcarbonyl.

[0122]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group, a carbonyl group and an oxygen atom, "the group formed of a cyclic hydrocarbon group, an alkylene group, a carbonyl group and an oxygen atom" means a group composed of the above-described group, which is formed of a cyclic hydrocarbon group, an alkylene group and a carbonyl group, and an oxygen atom, for example, cyclohexadienylmethylcarbonyloxy and phenylethylcarbonyloxy, while "the group formed of a heterocyclic group, an alkylene group, a carbonyl

group and an oxygen atom" means a group composed of the above-described group, which is formed of a heterocyclic group, an alkylene group and a carbonyl group, and an oxygen atom such as furylmethylcarbonyloxy, thienylethylcarbonyloxy and pyridylpropylcarbonyloxy.

[0123]

As examples of a substituent which can be substituted for the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group, those as shown below in Class (3) can be given. The number of the substituents which can be replaced is 1 to 3.

[0124]

Class (3):

- a hydroxyl group,
- an alkyl group,
- an alkoxyl group,
- a hydroxyalkyl group,
- an alkoxyalkyl group,
- a halogen atom,
- a cyano group,
- a nitro group,
- a carboxyl group,
- an alkoxycarbonyl group,
- a formyl group,
- a heteroaryl group,

a heteroarylalkyl group,
 an alkylimino group,
 an amidino group,
 a guanidino group,
 an amino(hydroxyimino)alkyl group,
 an amino(alkoxyimino)alkyl group,
 an amino(aryloxyimino)alkyl group,
 an amino group which may have 1 or 2 substituents,
 an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,
 an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents, and
 an oxygen atom.

[0125]

A description will next be made of the substituents which can be replaced for the saturated or unsaturated 5-

or 6-membered cyclic hydrocarbon or heterocyclic group in Class (3).

[0126]

The alkyl group, alkoxyl group, hydroxyalkyl group, alkoxyalkyl group, halogen atom, alkoxycarbonyl group, aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, and aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents have the same meanings as described above.

[0127]

The "heteroaryl group" means a monovalent aromatic group having at least one hetero atom. Examples include pyridyl, furyl and thienyl.

[0128]

The "heteroarylalkyl group" means a group formed of the above-described heteroaryl group and a linear, branched or cyclic C₁₋₆ alkylene group. Examples include pyridylmethyl, furylethyl and thienylmethyl.

[0129]

The "alkylimino group" means a divalent group formed of a linear, branched or cyclic C₁₋₆ alkyl group and a nitrogen atom. Examples include methylimino and ethylimino.

[0130]

The "amino(hydroxyimino)alkyl group" means a group having amino and hydroxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C₁₋₆ alkyl group. Examples include amino(hydroxyimino)methyl and amino(hydroxyimino)ethyl.

[0131]

The "amino(alkoxyimino)alkyl group" means a group having amino and alkoxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C₁₋₆ alkyl group. Here, the "alkoxyimino group" means a divalent group formed of the above-described alkoxyl group and an imino group. Examples of the amino(alkoxyimino)alkyl group include amino(methoxyimino)methyl and amino(ethoxyimino)methyl.

[0132]

The "amino(aryloxyimino)alkyl group" means a group having amino and aryloxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C₁₋₆ alkyl group. Here, the "aryloxyimino group" means a divalent group formed of aryl and imino groups. Examples of the aryl group usable here include phenyl, naphthyl, anthryl and phenanthryl. Examples of the amino(aryloxyimino)alkyl

group include amino(phenoxyimino)methyl and amino(naphthyloxyimino)methyl.

[0133]

The "aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of an amino group having a substituent, a linear, branched or cyclic C₂₋₆ alkylene group and an oxygen atom. Examples of the aminoalkyloxy group include aminoethyloxy and aminopropoxy. Examples of the group which can be substituted for the amino moiety include those exemplified above.

[0134]

In the case of the cyclic hydrocarbon group, an oxygen atom can serve as a substituent when the corresponding keto compound is formed, while, in the case of the heterocyclic group or dicyclic or tricyclic fused ring group, an oxygen atom can serve as a substituent when the oxygen atom is bonded to a nitrogen or sulfur atom forming the ring and the corresponding N-oxide or S-oxide or keto compound is formed.

[0135]

In the present invention, when R¹⁵ does not mean a C₁₋₃ alkylene or alkenylene group together with R¹⁶ or R¹⁷, preferred examples of R¹⁵ include a hydrogen atom, an alkyl group, a hydroxyalkyl group and a group A³-B³-.

[0136]

In R¹⁶ and R¹⁷, examples of the halogen atom include

fluorine, chlorine, bromine and iodine.

[0137]

The "alkyl group" means a linear, branched or cyclic C₁₋₈ alkyl group. Examples include methyl, ethyl, isopropyl, cyclopropyl, heptyl and octyl.

[0138]

The "hydroxyalkyl group" means a group formed of a hydroxyl group and a linear, branched or cyclic C₁₋₈ alkylene group. Examples include hydroxymethyl and hydroxyethyl.

[0139]

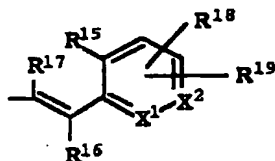
The "alkoxyalkyl group" means a group formed of the above-described alkyl group, an oxygen atom and a linear, branched or cyclic C₁₋₈ alkylene group. Examples include methoxymethyl, methoxyethyl and ethoxymethyl.

[0140]

When R¹⁶ or R¹⁷ forms a C₁₋₃ alkylene or alkenylene group together with R¹⁵, the following group:

[0141]

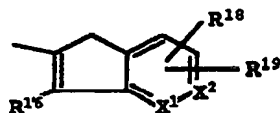
[Chemical formula 24]



means the following group:

[0142]

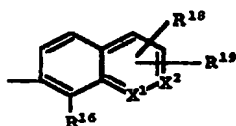
[Chemical formula 25]



[0143]

[Chemical formula 26]

or



[0144]

In the present invention, when R^{16} or R^{17} does not mean a C_{1-3} alkylene or alkenylene group together with R^{15} , a hydrogen atom and alkyl group are preferred as R^{16} or R^{17} .

[0145]

In the present invention, it is preferred that R^{15} and R^{16} or R^{17} are coupled together to form a C_{1-3} alkylene or alkenylene group.

[0146]

R^{18} and R^{19} each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, an alkenyl group, an alkynyl group which may be substituted with an alkylsilyl group as a protecting group, a trifluoromethyl group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group (with the proviso

that R^{18} and R^{19} do not represent a hydrogen atom at the same time).

[0147]

In R^{18} and R^{19} , the halogen atom, halogenoalkyl group, alkyl group, alkoxyl group, alkenyl group and aminoalkyl group mean have the same meaning as described above.

[0148]

The "alkylaminoalkyl group" means a group wherein the amino group of the aminoalkyl moiety have been substituted with 1 or 2 linear, branched or cyclic alkyl groups and examples include methylaminomethyl and ethylmethylaminomethyl.

[0149]

The "alkynyl group which may be substituted with an alkylsilyl group as a protecting group" means an alkynyl group which may be substituted with an alkylsilyl group such as trimethylsilyl, triethylsilyl, tertiary butyldimethylsilyl or dimethylphenylsilyl group as a protecting group.

[0150]

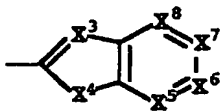
In the present invention, as R^{18} or R^{19} , a halogen atom and alkynyl group are preferred, with a chlorine atom, bromine atom and ethynyl group are particularly preferred.

[0151]

X^3 in the group:

[0152]

[Chemical formula 27]



means a nitrogen atom or a group $=C(R^{100})-$

(wherein, R^{100} represents a hydrogen atom, a halogen atom, an alkyl group, an alkoxy carbonyl group, an aralkyloxy carbonylalkyl group, an alkoxy carbonylalkyl group, a nitro group, an amino group which may have a protecting group or an aminoalkyl group which may have, at the amino moiety thereof, a protecting group).

[0153]

The halogen atom, alkyl group, alkoxy carbonyl group, aryloxy carbonylalkyl group, alkoxy carbonylalkyl group, aryloxy carbonylalkyl group in R^{100} have the same meanings as described above, respectively. The amino group which may have a protecting group or aminoalkyl group which may have, at the amino moiety thereof, a protecting group mean amino and aminoalkyl groups which may have an ordinarily known protecting group, respectively.

[0154]

X^4 represents an oxygen atom, a sulfur atom or a group $-N(R^{101})-$

(wherein R^{101} means a hydrogen atom, an alkyl group, an alkoxy carbonyl group, an aralkyloxy carbonyl group, an alkoxy-

carbonylalkyl group, an alkylsulfonyl group or an arylsulfonyl group).

[0155]

The alkyl group, alkoxycarbonyl group, aralkyloxycarbonyl group, alkoxycarbonylalkyl group, alkylsulfonyl group and arylsulfonyl group in R^{101} have the same meanings as described above, respectively.

[0156]

X^5 and X^8 each independently represents a nitrogen atom or a group $-C(R^{102})$ (wherein, R^{102} represents a hydrogen atom or a halogen atom) and the halogen atom in R^{102} has the same meaning as described above.

[0157]

X^6 and X^7 each independently represents a nitrogen atom or a group $-C(R^{103})-$ (wherein R^{103} represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group.

[0158]

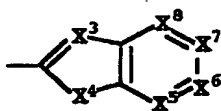
The halogen atom, halogenoalkyl group, alkyl group, alkoxy group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, aminoalkyl group, alkylaminoalkyl group, alkoxycarbonylamidino group in R^{103} have the same meanings as described above.

[0159]

It is preferred that the group:

[0160]

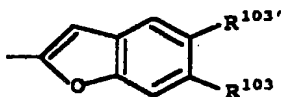
[Chemical formula 28]



means any one of the following groups:

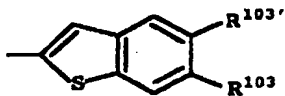
[0161]

[Chemical formula 29]



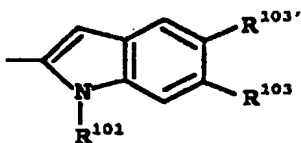
[0162]

[Chemical formula 30]



[0163]

[Chemical formula 31]



[wherein R^{101} and R^{103} have the same meanings as described above and $R^{103'}$ means those similar to R^{103}].

[0164]

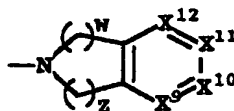
As R^{101} , a hydrogen atom is particularly preferred. It is preferred that either one of R^{103} and $R^{103'}$ represents a halogen atom, an alkynyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group, with the halogen atom, ethynyl group, amidino group, hydroxyamidino group and methoxycarbonylamidino group being particularly preferred.

[0165]

In the group:

[0166]

[Chemical formula 32]



X^9 and X^{12} each independently represents a nitrogen atom or a group $-C(R^{104})-$

(wherein R^{104} represents a hydrogen atom or a halogen atom) and the halogen atom as R^{104} is similar to that described above.

[0167]

X^{10} and X^{11} each independently represents a nitrogen atom or a group $-C(R^{105})-$ (wherein R^{105} represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxy group, an alkenyl group, an alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxy-carbonylamidino group.

[0168]

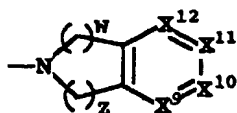
The halogen atom, halogenoalkyl group, alkyl group, alkoxy group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, aminoalkyl group, alkylaminoalkyl group and alkoxy-carbonylamidino group in R^{105} have the same meanings as described above.

[0169]

The group:

[0170]

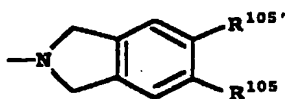
[Chemical formula 33]



preferably represents the following group:

[0171]

[Chemical formula 34]



[wherein R^{105} has the same meanings as described above and $R^{105'}$ is similar to that described as R^{105}].

[0172]

It is preferred that either one of R^{105} and $R^{105'}$ represents a halogen atom, an alkynyl group, an amidino group, a hydroxyamidino group or an alkoxy carbonylamidino group, with the halogen atom, ethynyl group, amidino group, hydroxyamidino group and methoxy carbonylamidino group being particularly preferred.

[0173]

<About the group Q^1 >

Q^1 represents a saturated or unsaturated dicyclic fused ring group which may have a substituent or a saturated or unsaturated tricyclic fused ring group which may have a substituent.

[0174]

The "saturated or unsaturated, dicyclic fused ring group which may have a substituent" or "saturated or unsaturated, tricyclic fused ring group which may have a substituent" has the same meaning as defined in the description of the group Q^A . More specifically, it means: 1) a

group obtained by the condensation of saturated or unsaturated 5- or 6-membered cyclic hydrocarbon groups which may have a substituent, 2) a group obtained by the condensation of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and 3) a group obtained by the condensation of saturated or unsaturated 5- or 6-membered heterocyclic groups which may have a substituent. Examples of the group 1) include indenyl, indanyl, naphthyl, tetrahydronaphthyl, anthryl and phenanthryl; those of the group 2) include benzofuranyl, indolyl, indolinyl, quinolyl, benzodiazinyl and tetrahydroisoquinolyl; and those of the group 3) include naphthyridinyl, furanopyridyl, thienopyridyl, tetrahydrothienopyridyl, pyrazolopyridyl, thiazolopyridyl, tetrahydrothiazolopyridyl, thiazolopyrazyl, tetrahydrothiazolopyrazyl, thiazolopyridazyl and tetrahydropyridinopyridyl groups.

[0175]

Examples of the substituent which can be replaced for the above-described saturated or unsaturated dicyclic fused ring group, or saturated or unsaturated tricyclic fused ring group include the groups shown in the below-described Class (4). The number of the replaceable substituents ranges from 1 to 7.

[0176]

Class (4):

- a hydroxyl group,
- an alkyl group,
- an alkenyl group,
- a halogenoalkyl group,
- a halogenoalkenyl group,
- an alkoxyl group,
- a hydroxyalkyl group,
- an alkoxyalkyl group,
- a halogen atom,
- a cyano group,
- a nitro group,
- a carboxyl group,
- an alkoxycarbonyl group,
- a formyl group,
- a heteroaryl group,
- a heteroarylalkyl group,
- an alkylimino group,
- an amidino group,
- a guanidino group,
- an amino(hydroxyimino)alkyl group,
- an amino(alkoxyimino)alkyl group,
- an amino(aryloxyimino)alkyl group,
- an amino group which may have 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an oxygen atom,

a trifluoromethylsulfonyloxy group,

a trifluoromethylsulfonyloxyalkenyl group,

a boric acid group ($-B(OH_2)$),

a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have 1 to 3 substituents selected from the group consisting of halogen, hydroxyl, amino, alkoxyl, alkyl, cyano, nitro, carboxyl, alkoxycarbonyl and aminocarbonyl, and

a saturated or unsaturated 5- or 6-membered heterocyclic group which may have 1 to 3 substituents selected from the group consisting of halogen, hydroxyl, amino, alkoxyl,

alkyl, cyano, nitro, carboxyl, alkoxy carbonyl and aminocarbonyl.

[0177]

The substituents in Class (4) have the same meanings as described in Classes (1) to (3) of the description of the group Q^A .

[0178]

In the present invention, preferred examples of Q^1 include a thienopyridyl group which may have a substituent, a tetrahydrothienopyridyl group which may have a substituent, a thiazolopyridyl group which may have a substituent, and a tetrahydrothiazolopyridyl group which may have a substituent.

[0179]

<About the group Q^2 >

The group Q^2 represents a single bond, an oxygen atom, a sulfur atom, a linear or branched C_{1-6} alkylene group, a linear or branched C_{2-6} alkenylene group, a linear or branched C_{2-6} alkynylene group,

a group $-N(R^1)-CO-$

(wherein, R^1 represents a hydrogen atom or an alkyl group),

a group $-N(R^2)-(CH_2)_m-$

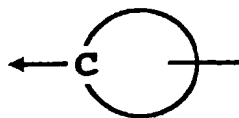
(wherein R^2 represents a hydrogen atom or an alkyl group

and m stands for an integer of 0 to 6), or

a group:

[0180]

[Chemical formula 35]



(which represents a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent,

a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent or

a divalent, saturated or unsaturated dicyclic fused ring group which may have a substituent and $\leftarrow C$ means the bonding of the carbon atom of this group to Q^1),

[0181]

In Q^2 , examples of the linear or branched C_{1-6} alkylene group include methylene, ethylene, trimethylene, propylene, tetramethylene, butylene, pentamethylene and hexamethylene.

[0182]

Examples of the linear or branched C_{2-6} alkenylene group include vinylene, propenylene, butenylene and pentenylene. There is no particular limitation on the position of the double bond.

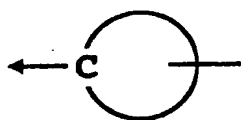
[0183]

Examples of the linear or branched C_{2-6} alkynylene group include propynylene, butynylene, pentynylene and hexynylene.

The group of the following formula:

[0184]

[Chemical formula 36]



means a divalent, saturated or unsaturated 5- or 6-membered cyclic group which may have one or more hetero atoms which may have a substituent and $\leftarrow C$ means the bonding of the carbon atom of this group to Q^1 . Examples of the group include cyclohexylene, cyclohexenylene, phenylene, pyrrolediyl and thiophenediyl.

[0185]

The alkyl group in R^1 or R^2 of the group $-N(R^1)-CO-$ or $-N(R^2)-(CH_2)_m-$ means a linear, branched or cyclic C_{1-6} alkyl group. Examples include methyl, ethyl, isopropyl and cyclopropyl. As the group $-N(R^1)-CO-$, a group $\leftarrow N(R^1)-CO-$ (wherein \leftarrow means the bonding of the nitrogen atom of this group to Q^1) is preferred, while as the group $-N(R^2)-(CH_2)_m-$, a group $\leftarrow N(R^2)-(CH_2)_m-$ (wherein \leftarrow means the bonding of the nitrogen atom of this group to Q^1) is preferred.

[0186]

In the present invention, Q^2 preferably represents a single bond, a carbonyl group, a phenylene group, a cyclohexylene group or a cyclohexenylene group.

[0187]

<About Q³>

In R³, R⁴, R⁵, R⁶, R⁷, R⁸, R¹⁰ and R¹¹ as the substituents in Q³, the alkyl, alkoxyl, alkoxyalkyl, hydroxyalkyl, hydroxyalkyloxy, hydroxyalkylcarbonyl, hydroxyalkylsulfonyl, formylalkyl, formylalkylcarbonyl, formylalkylsulfonyl, alkylcarbonyl, alkylsulfonyl, alkylcarbonylalkyl, alkylsulfonylalkyl, carboxyalkyl, carboxyalkylcarbonyl, carboxyalkylsulfonyl, carboxyalkylcarbonylalkyl, carboxyalkylsulfonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylalkylsulfonyl, amino which may have 1 to 2 substituents, aminoalkyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyloxy which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkylcarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkylcarbonyloxy which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonylalkyl which may have, at the amino moiety thereof, 1 or 2 substituents, and aminocarbonylalkyloxy which may have, at the amino moiety thereof, 1 or 2 substituents have the same meanings as described above in R¹⁵ of the description of the group Q^A.

[0188]

The "alkoxyalkyloxy group" means a group formed of the above-described alkoxyalkyl group and an oxygen atom and examples include methoxymethyloxy, methoxyethyloxy and ethoxymethyloxy.

[0189]

The "carboxyalkyloxy group" means a group formed of the above-described carboxyalkyl group and an oxygen atom and examples include carboxymethoxyl and carboxyethoxyl.

[0190]

The "alkoxycarbonylalkyloxy group" means a group formed of the above-described alkoxycarbonylalkyl group and an oxygen atom and examples include methoxycarbonylethyl and ethoxycarbonylethyl.

[0191]

In the group A^1-B^1- , A^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent. Here, examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has, similar to a cyclopentenyl group, various structural isomers they are all embraced in it.

[0192]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has plural structural isomers as the pyranyl group, they are all embraced in it.

[0193]

B¹ represents a single bond, carbonyl group, alkylene group, carbonylalkyl group, a group -NHCO- or a group -NHCO-(C₁₋₆ alkylene).

[0194]

Examples of the group A¹-B¹- include the following groups:

a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and a carbonyl group, and

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkylene group.

[0195]

Each of R^3 and R^4 , R^5 and R^6 , R^7 and R^8 , and R^{10} and R^{11} are coupled together with a carbon atom which constitutes the ring and represents a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent. Here, examples of the saturated or unsaturated 5- or 7-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has, similar to a cyclopentenyl group, various structural isomers, they are all embraced in it.

[0196]

The saturated or unsaturated 5- to 7-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, mor-

pholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has, similar to a pyranyl group, plural structural isomers, they are all embraced in it.

[0197]

In R^9 or R^{12} as the substituent in Q^3 , the alkyl, hydroxyalkyl, alkoxyl, hydroxyalkylcarbonyl, hydroxyalkylsulfonyl, alkoxylalkyl, alkoxylalkylcarbonyl, alkoxylalkylsulfonyl, formylalkyl, formylalkylcarbonyl, formylalkylsulfonyl, alkylcarbonyl, alkylsulfonyl, alkylcarbonylalkyl, alkylsulfonylalkyl, carboxyalkylcarbonyl, carboxyalkylsulfonyl, carboxyalkylcarbonylalkyl, carboxyalkylsulfonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylalkylsulfonyl, amino which may have 1 to 2 substituents, aminoalkyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyloxy which may have, at the amino moiety thereof, 1 to 2 substituents, aminoalkylcarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyloxycarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonylalkyl which may have, at the amino moiety thereof, 1 or 2 substituents, and aminocarbonyloxyalkyl which may have, at the amino moiety thereof, 1 or 2 substituents have the same meanings as described in Q^A .

[0198]

In the group A^2-B^2- , A^2 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent. Here, examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has, similar to a cyclopentenyl group, plural structural isomers, they are all embraced in it.

[0199]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has, similar to a pyranyl group, plural structural isomers, they are all embraced in it.

[0200]

B² represents a single bond, carbonyl group, alkylene group, carbonylalkyl group, a group -NHCO- or a group -NHCO-(C₁₋₆ alkylene).

[0201]

Examples of the group A²-B²- include the following groups:

a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a carbonyl group, and

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkylene group.

[0202]

R⁹ and R⁷, R⁹ and R⁸, R¹² and R¹⁰, and R¹² and R¹¹ are each coupled together with the carbon atom which constitutes the ring and the nitrogen atom to which R⁹ or R¹² has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent. Here, the saturated or unsaturated 5- to 7-membered heterocyclic group is a cyclic group which has at least one nitrogen atom and may have a hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic

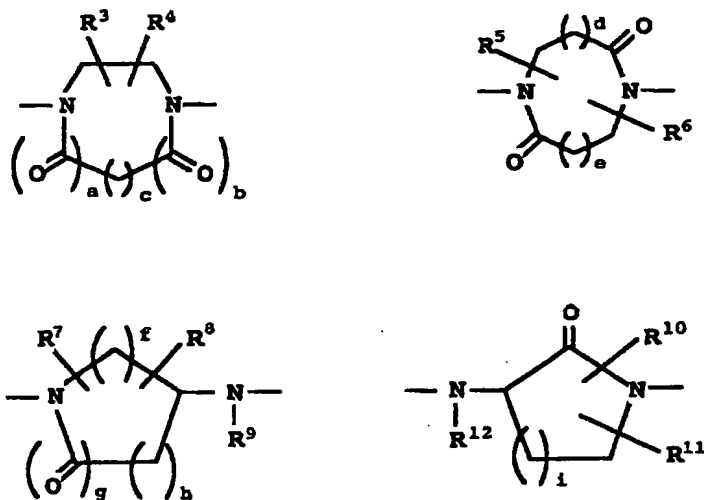
clic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, triazolyl and triazinyl. Where the group has, similar to a pyranyl group, plural structural isomers, they are all embraced in it.

[0203]

In the present invention, Q^3 represents a group of the following formula:

[0204]

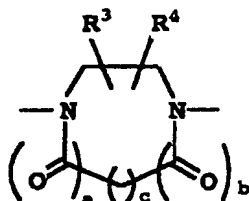
[Chemical formula 37]



(wherein R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , a , b , c , d , e , f , g , h and i have the same meanings as described above). Preferred as Q^3 is a group of the following formula:

[0205]

[Chemical formula 38]



(wherein R^3 , R^4 , a , b and c have the same meanings as described above), of which the group wherein:

R^3 and R^4 each independently represents

- a hydrogen atom,
- a carboxyl group,
- a carboxyalkyl group,
- an alkoxycarbonyl group,
- an alkoxycarbonylalkyl group,
- a carboxyalkylaminocarbonyl group,
- a carboxyalkylaminocarbonylalkyl group,
- an alkoxycarbonylalkylaminocarbonyl group,
- an alkoxycarbonylalkylaminocarbonylamino group,
- a carbamoyl group,
- a monoalkylcarbamoyl group,
- a dialkylcarbamoyl group,
- a carbamoylalkyl group,
- a monoalkylcarbamoylalkyl group,
- a dialkylcarbamoylalkyl group,
- a morpholinylcarbonyl group

a morpholinylcarbonylalkyl group,

a tetrazolylaminocarbonyl group,

a tetrazolylaminocarbonylalkyl group,

a tetrazolylalkyl group,

a tetrazolylalkylaminocarbonyl group, or

a tetrazolylalkylaminocarbonylamino group,

a stands for 0, b stands for 0 and c stands for 2 is more preferred.

[0206]

<About the group T^1 >

T^1 represents a carbonyl group,

a group $-CH(R^{13})-$

(in which R^{13} represents a hydrogen atom, an alkyl group, a hydroxyalkyl group, an alkoxyalkyl group, a carboxyalkyl group, an alkoxycarbonylalkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent) or

a group $-C(=NOR^{14})-$

(in which R^{14} represents a hydrogen atom, an alkyl group, a carboxyalkyl group, an alkoxycarbonyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent).

[0207]

Here, in R^{13} and R^{14} , the alkyl, carboxyalkyl, alkoxy-carbonyl, aryl, aralkyl, heteroaryl, heteroarylalkyl and aminoalkyl which may have, at the amino moiety thereof, a substituent have the same meanings as described in Q^A . In the present invention, a carbonyl group is preferred as T^1 .

[0208]

The sulfonyl derivative of the present invention has optical isomers or stereoisomers based on an asymmetric carbon atom. These optical isomers and stereoisomers and mixtures thereof are all embraced in the present invention.

[0209]

Although there is no particular limitation imposed on the salt of the sulfonyl derivative according to the present invention insofar as it is a pharmaceutically acceptable salt. Specific examples include salts of a mineral acid such as hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate and sulfate, salts of an organic sulfonic acid such as benzoate, methanesulfonate, 2'-hydroxyethanesulfonate and p-toluenesulfonate and salts of an organic carboxylic acid such as acetate, propanoate, oxalate, malonate, succinate, glutarate, adipate, tartrate, maleate, malate and mandelate. There is no particular limitation imposed on the solvate insofar as it is pharmaceutically acceptable. Specific examples include hydrates and ethanolates.

[0210]

The following are the preferred compounds as the sulfonyl derivative of the present invention.

[0211]

1-[[(6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[[(6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[[(2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[[(2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[(7-Aminomethylnaphthalen-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

[0212]

1-[(7-Aminomethylnaphthalen-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[(6-Aminomethylnaphthalen-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(isoquinolin-7-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(quinolyl-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4-hydroxyquinolin-2-yl)carbonyl]piperazine

[0213]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(8-hydroxyquinolin-7-yl)carbonyl]piperazine

1-[(Benzimidazole)-5-yl-carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[(Benzimidazol-5-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(E)-4-Chlorostyrylsulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0214]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[trans-3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]carbamoyl]piperazine

[0215]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine

2-Carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine

[0216]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-methy-N-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(1-pyrrolin-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

[0217]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(1-pyrrolin-2-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-formyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridinium iodide

[0218]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin N-oxide

2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

[0219]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-3-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

1-[(E)-4-Chlorostyrylsulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(E)-4-Chlorostyrylsulfonyl]-4-[6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

(3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamide]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]pyrrolidine

[0220]

(3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamide]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]pyrrolidine

(3S)-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-

yl)methyl]amino]pyrrolidine

(3S)-3-[(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]homopiperazine

4-[(6-Chloronaphthalen-2-yl)sulfonamide]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperidine

[0221]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethylbenzofuran-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-aminohydroxyiminomethylbenzothiophen-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]piperazine

6-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide

[0222]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-
1-[(6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-
yl)carbonyl]piperazine

1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

[0223]

1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5,6,7,8-
tetrahydro-1,6-naphthylidin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-
5,6,7,8-tetrahydro-1,6-naphthylidin-2-
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-
tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-
yl)carbonyl]piperazine

[0224]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(1,5-dimethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl)carbonyl]piperazine

[0225]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(3-hydroxy-6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-3-hydroxy-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydroxazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-
1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-
2-yl)carbonyl]piperazine

2,6-Bis(carbamoylmethyl)-4-[(5-chloroindol-2-
yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
[0226]

cis-2,6-Bis(carbamoylmethyl)-4-[(5-chloroindol-2-
yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroisindol-2-yl)sulfonyl]-2-(N-
methylcarbamoyl)-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-
yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-
methylcarbamoyl)-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
[[(morpholin-4-yl)carbonyl]methyl]piperazine

[0227]

N-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazin-2-yl]carbonyl]glycine ethyl ester

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-(morpholin-4-yl)carbamoyl]piperazine

Ethyl N'-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetate

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine

4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]morpholine

[0228]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

Methyl [4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetate

2-[[N-(tert-Butoxy)amino]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetamide

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-isopropyl)carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
[0229]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(piperidin-1-yl)carbonyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

N'-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetic acid
[0230]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[N-(tetrahydropyran-2-yloxy)]carbamoyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-hydroxamic acid

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-hydroxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Bromonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(7-Amidinonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0231]

1-[(6-Amidinonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[7-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

1-[(7-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0232]

1-[(6-Ethynyl-naphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Bromoindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Amidinoindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Amidinoindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0233]

1-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl]sulfonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]piperazine

1-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0234]

1-[(6-Amidinobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[[6-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

[0235]

4-[(5-Amidinoisindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

[0236]

2-[[4-[(5-Bromoindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-(Carbamoyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-(Carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2,6-Bis(carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

[0237]

2-[[2-[(Tetrazol-5-ylmethyl)amino]carbonyl]-4-(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-[2-(Tetrazol-5-yl)ethyl]-4-(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-[(Morpholin-4-ylcarbonyl)methyl]-4-(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(carbamoylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

[0238]

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[tetrazol-5-yl)amino]carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[tetrazol-5-ylmethyl)amino]carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[tetrazol-5-ylamino)carbonyl]methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

[[[(tetrazol-5-ylmethyl)amino]carbonyl]methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

(tetrazol-5-ylmethyl)piperazine

[0239]

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-

(tetrazol-5-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(morpholin-4-ylcarbonyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[(morpholin-4-ylcarbonyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylisoindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0240]

4-[(5-Chloroisoindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Carbamoylmethyl)-4-[(5-chloroisoindol-2-yl)sulfonyl]-
1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

2-(Carbamoylmethyl)-4-[(5-ethynylisoindol-2-
yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-
c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroisoindol-2-yl)sulfonyl]-2-(N-
methylcarbamoylmethyl)-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroisoindol-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
(N,N-dimethylcarbamoylmethyl)piperazine

[0241]

4-[(5-Chloroisoindol-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(5-Bromoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
(morpholinocarbonylmethyl)piperazine

4-[(5-Ethynylisoindol-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
[(morpholin-4-ylcarbonyl)methyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-
4,5,6,7-tetrahydroxazolo[4,5-c]pyridin-2-
yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-
1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-
2-yl)carbonyl]piperazine

[0242]

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-
methylcarbamoylmethyl)-1-[(6,7-dimethyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-
(morpholinocarbonylmethyl)-1-[(6,7-dimethyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-
(morpholinocarbonylmethyl)-1-[(6,7-dimethyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Bromoindol-2-yl)sulfonyl]-2-
(morpholinocarbonylmethyl)-1-[(6,7-dimethyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis(carbamoylmethyl)-4-[(5-chloroindol-2-
yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0243]

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-
1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-
2-yl)carbonyl]piperazine

2,6-Bis(carbamoylmethyl)-1-[(6,7-dimethyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-
ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-
 [[(ethoxycarbonylmethyl)aminocarbonyl]methyl]-1-[(6,7-
 dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-
 [[(ethoxycarbonylmethyl)aminocarbonyl]methyl]-1-[(6-methyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-
 [[(carboxymethyl)aminocarbonyl]methyl]-1-[(6,7-dimethyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazine

[0244]

4-[(5-Chloroindol-2-yl)sulfonyl]-2-
 [[(carboxymethyl)aminocarbonyl]methyl]-1-[(6-methyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
 [[[tetrazol-5-yl)methyl]aminocarbonyl]methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
 [[[tetrazol-5-yl)methyl]aminocarbonyl]methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
 [(tetrazol-5-yl)methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

[0245]

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(2-oxopyrrolidin-1-yl)methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(2-oxopyrrolidin-1-yl)methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxopyrrolidin-1-yl)ethyl]piperazine

[0246]

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxopyrrolidin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(4-hydroxy-2-oxopyrrolidin-1-yl)methyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(4-hydroxy-2-oxopyrrolidin-1-yl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(4-hydroxy-2-oxopyrrolidin-1-yl)ethyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(4-hydroxy-2-oxopyrrolidin-1-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0247]

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(2,5-dioxopyrrolidin-1-yl)methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(2,5-dioxopyrrolidin-1-yl)methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

2,6-Bis[2-(4-hydroxy-2-oxopyrrolidin-1-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0248]

2,6-Bis[2-(2-oxopyrrolidin-1-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis[2-(tetrazol-5-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis[(tetrazol-5-yl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis[(N-methylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis[(2,5-dioxopyrrolidin-1-yl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0249]

2,6-Bis[2-(2,5-dioxopyrrolidin-1-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[7-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]piperazine-2-carboxylic acid

[0250]

4-[(7-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

[0251]

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

[0252]

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]piperazine-2-carboxylic acid

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[(6-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

1-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

[0253]

4-[[6-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-(N-methoxycarbonylamidino)benzo[b]thien-

2-yl)sulfonyl]piperazine-2-carboxylic acid

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

[0254]

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]piperazine-2-carboxylic acid

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl] 4-[[7-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

[0255]

4-[(7-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0256]

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
[0257]

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

4-[(5-Amidinoisindol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0258]

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]piperazine

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazine

[0259]

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

[0260]

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl]sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

[0261]

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-

(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]-2-
[(tetrazol-5-yl)methyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
[(tetrazol-5-yl)methyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-
yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-
c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-
yl)methyl]piperazine

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-
yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-
c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-
yl)methyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(tetrazol-
5-yl)methyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-
c]pyridinium iodide

[0262]

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(tetrazol-5-
yl)methyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-
c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
[2-(tetrazol-5-yl)ethyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
[2-(tetrazol-5-yl)ethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

[0263]

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

[0264]

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-

yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

[0265]

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-

yl)ethyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

[0266]

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

[0267]

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

[0268]

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

[0269]

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazin-1-yl]carbonyl]-6-

methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

[0270]

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

[0271]

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-
1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]-2-[N-[(tetrazol-5-
yl)methyl]carbamoylmethyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-
1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]-2-[N-[(tetrazol-5-
yl)methyl]carbamoylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-
yl]sulfonyl]-2-[N-[(tetrazol-5-
yl)methyl]carbamoylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-
yl]sulfonyl]-2-[N-[(tetrazol-5-
yl)methyl]carbamoylmethyl]piperazine

[0272]

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-
[N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-
yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-
c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-
yl)methyl]carbamoylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]

benzo[b]thien-2-yl]sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

[0273]

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0274]

2-(Ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0275]

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(ethoxycarbonylmethyl)-4-[[5-(N-

methoxycarbonylamidino)indol-2-yl)sulfonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(ethoxycarbonylmethyl)-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0276]

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(ethoxycarbonylmethyl)-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Ethoxycarbonylmethyl)-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0277]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]piperazin-2-acetic acid

[0278]

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

[0279]

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl]sulfonyl]piperazin-2-acetic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]piperazin-2-acetic acid

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

[0280]

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]piperazin-2-acetic acid

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

2-[[2-(Carboxymethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

[0281]

2-[[2-(Carboxymethyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0282]

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0283]

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(N-methylcarbamoyl)methyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl]sulfonyl]piperazine

2-[(N-Methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-

(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[(N-Methylcarbamoyl)methyl]1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]piperazine

[0284]

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[(N-methylcarbamoyl)methyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[2-[(N-Methylcarbamoyl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-

methylthiazolo[5,4-c]pyridinium iodide

2-[[2-[(N-methylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

[0285]

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0286]

4-[(5-Amidinoindol-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl)sulfonyl]piperazine

[0287]

2-[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0288]

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0289]

2-[[N-(Carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Carboxymethyl)carbamoyl]methyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0290]

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-
2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-
2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

2-[[N-(Carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-
[[5-(N-methoxycarbonylamidino)indol-2-
yl]sulfonyl]piperazine

2-[[N-(Carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-
[[6-[N-(methoxycarbonyl)amidino]indol-2-
yl]sulfonyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-[[N-
(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0291]

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-
yl]sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]piperazine

2-[[N-(Carboxymethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-[[N-(carboxymethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-2-[[N-(carboxymethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Carboxymethyl) carbamoyl]methyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0292]

2-[[2-[[N-(Carboxymethyl) carbamoyl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-[[N-(Carboxymethyl) carbamoyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

[0293]

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

[0294]

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl) carbonyl]-2-[(morpholin-4-yl) carbonylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[5-(N-methoxycarbonylamidino) indol-2-

yl] sulfonyl]-2-[(morpholin-4-yl) carbonylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[6-[N-(methoxycarbonyl) amidino] indol-2-

yl] sulfonyl]-2-[(morpholin-4-yl) carbonylmethyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[(morpholin-4-yl) carbonylmethyl]piperazine

4-[[5-[(Amino) (hydroxyimino) methyl] benzo[b]thien-2-yl] sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[(morpholin-4-yl) carbonylmethyl]piperazine

[0295]

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[5-[N-

(methoxycarbonyl) amidino] benzo[b]thien-2-yl] sulfonyl]-2-

[(morpholin-4-yl) carbonylmethyl]piperazine

4-[(5-Amidinoisoindol-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-

[(morpholin-4-yl) carbonylmethyl]piperazine

4-[[5-[(Amino) (hydroxyimino) methyl] isoindol-2-yl] sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-

c]pyridin-2-yl) carbonyl]-2-[(morpholin-4-

yl) carbonylmethyl]piperazine

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

[0296]

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-cyano-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

1-[(7-Carbamoyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-dimethylamino-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-cyano-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

[0297]

1-[(7-Carbamoyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-dimethylamino-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-cyano-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[[(ethoxycarbonyl)methyl]amino]carbonyl]methyl]piperazine

1-[(7-Carbamoyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-

[[[(ethoxycarbonyl)methyl]amino]carbonyl]methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-dimethylamino-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

[[[(ethoxycarbonyl)methyl]amino]carbonyl]methyl]piperazine

[0298]

2-[[[(Carboxymethyl)amino]carbonyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(7-cyano-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(7-Carbamoyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

[[[(carboxymethyl)amino]carbonyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

2-[[[(Carboxymethyl)amino]carbonyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(7-dimethylamino-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[7-[(dimethylamino)methyl]benzothiazol-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[7-[(dimethylaminomethyl)methyl]thiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

[0299]

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[7-[(dimethylamino)methyl]-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[7-[(morpholin-4-yl)methyl]benzothiazol-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[6-(morpholin-4-yl)-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[7-(piperidin-1-yl)benzothiazol-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[6-(piperidin-1-yl)-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

[0300]

In the present invention, in addition to the above-exemplified compounds, salts thereof and solvates thereof can be mentioned as preferred examples.

[0301]

The process for the preparation of the sulfonyl derivative of the present invention will next be described.

[0302]

The sulfonyl derivative or salt thereof, or solvate thereof according to the present invention can be prepared by using general, conventionally-known chemical processes in combination. Typical synthesis processes will be described subsequently.

[0303]

Upon synthesis of the sulfonyl derivative of the present invention, when it is necessary to protect a substituent such as nitrogen atom, hydroxyl group or carboxyl group, it may be protected with an ordinary, conventionally-known protecting group which can be removed as needed. Such a protecting group can be removed at need by the synthesis process ordinarily employed in the organic chemistry which will be described below.

[0304]

The starting materials necessary for the synthesis can be obtained by the synthesis process ordinarily employed in the organic chemistry and such a process will be described in Referential Examples. The starting materials for the sulfonyl

derivative of the present invention can also be synthesized by the application of the process described in Referential Examples.

[0305]

A description will next be made of a protecting group for the substituent such as nitrogen atom, hydroxyl group or carboxyl group and deprotection process thereof.

[0306]

As a protecting group for the nitrogen atom in an amino or alkylamino group, ordinary acyl-type protecting groups are suited. Examples include alkanoyl groups such as acetyl, alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl and tertiary butoxy carbonyl, arylmethoxycarbonyl groups such as benzyloxycarbonyl, paramethoxybenzyloxycarbonyl and para-(ortho-)nitrobenzyloxycarbonyl groups, arylmethyl groups such as benzyl and triphenylmethyl and aroyl groups such as benzoyl. The removing process of such a protecting group differs with the chemical properties of the protecting group adopted. For example, the acyl-type protecting group such as alkanoyl, alkoxycarbonyl or aroyl can be removed by hydrolysis using an appropriate base such as alkali metal hydroxide, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide.

[0307]

The substituted methoxycarbonyl type protecting group such as tertiary butoxycarbonyl or paramethoxybenzyloxycarbonyl can be removed by using an

appropriate acid, for example, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. The arylmethoxycarbonyl group such as benzyloxycarbonyl, paramethoxybenzyloxycarbonyl or para-(ortho-)nitrobenzyloxycarbonyl, or the arylmethyl group such as benzyl can be removed by hydrogenolysis in the presence of a palladium-carbon catalyst. The benzyl group can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium, whereby conversion into a nitrogen-hydrogen bond can be effected. The triphenylmethyl group can be removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. It can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium or by hydrogenolysis in the presence of a palladium-carbon catalyst.

[0308]

In addition to the above-described amino-protecting group, a phthaloyl type protecting group can be adopted for a primary amino group and it can be removed using hydrazine, dimethylaminopropylamine or the like.

[0309]

As the protecting group suited for a hydroxyl group, there are acyl type and ether type ones. Examples of the acyl type protecting group include alkanoyl groups such as acetyl and

aroyl groups such as benzoyl, while those of the ether type protecting group include arylmethyl groups such as benzyl, silyl ether groups such as tertiary butyl dimethylsilyl, methoxymethyl and tetrahydropyranyl. The removal of such a protecting group differs with the chemical properties of the protecting group adopted. For example, the acyl group such as alkanoyl or aroyl can be removed by the hydrolysis using an appropriate base such as an alkali metal hydroxide, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide. The arylmethyl type protecting group can be removed by the hydrogenolysis using a palladium-carbon catalyst. The silyl group such as tertiary butyl dimethylsilyl can be removed using a hydrofluoride such as tetrabutyl ammonium fluoride. The methoxymethyl or tetrahydropyranyl group can be removed using acetic acid, hydrochloric acid or the like. The hydroxyl group substituted for an aryl group can be protected with a methyl group and deprotection can be carried out using a Lewis acid such as aluminum chloride, boron trifluoride or phosphorus tribromide, trimethylsilyl iodide or hydrogen bromide.

[0310]

A carboxyl group can be protected by the esterification of it. A methyl or ethyl ester can be deprotected by the hydrolysis using an appropriate base such as alkali metal hydroxide, e.g., lithium hydroxide, sodium hydroxide or potassium hydroxide, while from a tertiary butyl ester, the tertiary butyl group can be removed by treating with

trifluoroacetic acid or hydrochloric acid. From an arylmethyl type ester such as benzyl, the arylmethyl group can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst.

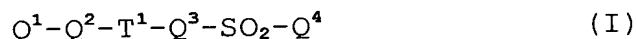
[0311]

[Preparation process-1]

A process for preparing a sulfonyl derivative represented by the following formula (I):

[0312]

[Chemical formula 40]



[wherein Q^1 , Q^2 , Q^3 , Q^4 and T^1 have the same meanings as described above], which comprises sulfonylating the nitrogen atom of Q^{3a} of the compound represented by the following formula (Ia):

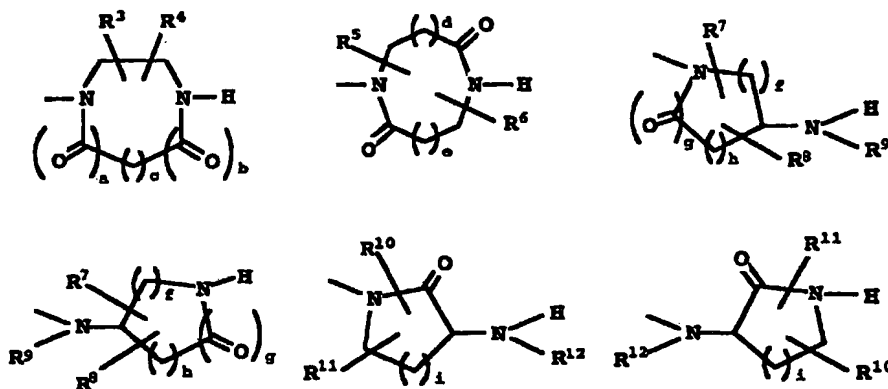
[0313]



[wherein Q^1 , Q^2 and T^1 have the same meanings as described above and Q^{3a} represents any one of the groups represented by the following formulas:

[0314]

[Chemical formula 39]



(in which R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², a, b, c, d, e, f, g, h and i have the same meanings as described above)]
with a sulfonic acid halide represented by the following formula
(IIa):

[0315]



[wherein Q⁴ has the same meaning as described above and Halo represents a halogen atom such as chlorine, bromine or iodine].

[0316]

<Synthesis of the compound of the formula (Ia)>

The compound of the formula (Ia) can be synthesized by a series of procedures in accordance with the known technique.

[0317]

For example, a compound of the following formula (Ib):

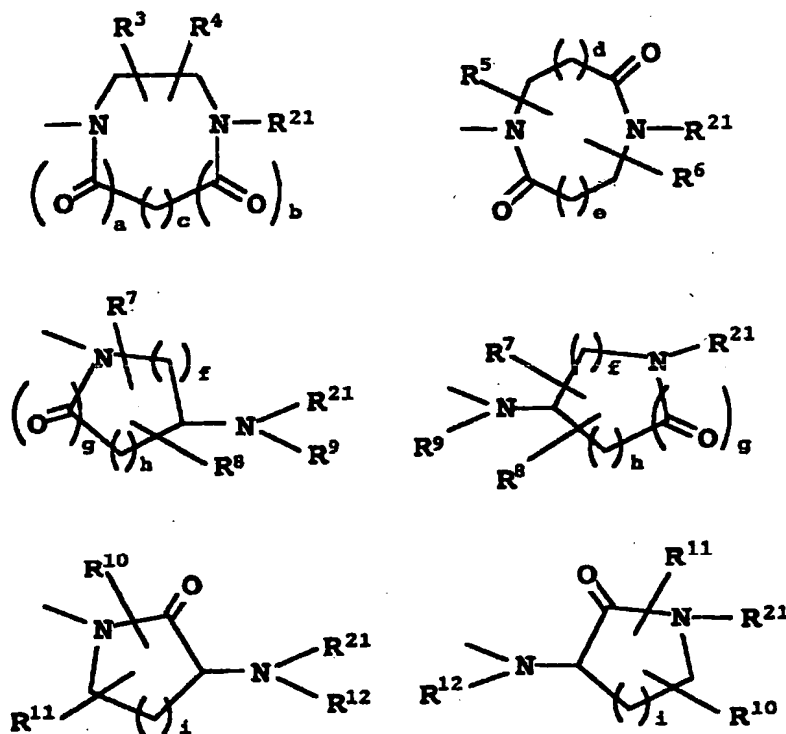
[0318]



[wherein Q¹, Q² and T¹ have the same meanings as described above and Q^{3b} represents any one of the following groups:

[0319]

[Chemical formula 41]



(wherein R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , a , b , c , d , e , f , g , h and i have the same meanings as described above and R^{21} represents an ordinary nitrogen protecting group such as tertiary butoxycarbonyl, benzyloxycarbonyl, paramethoxybenzyloxycarbonyl, paranitrobenzyloxycarbonyl or benzyl)] can be synthesized by acylating the nitrogen atom of the compound - which can be synthesized in a conventionally known manner or by application thereof and is represented by the following formula (IIIa):



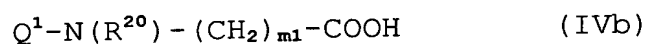
(wherein Q^{3b} has the same meaning as described above) - to which

the hydrogen atom of Q^{3b} has been bonded, with a carboxylic acid in an activated form represented by any one of the following formulas (Iva) to (IVd):

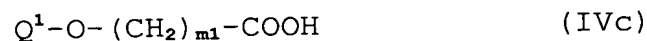
[0320]



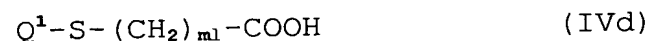
[0321]



[0322]



[0323]

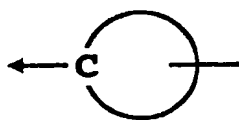


[0324]

[wherein Q^1 has the same meaning as described above, R^{20} represents an ordinary nitrogen protecting group such as linear or branched alkylkylene, tertiary butoxycarbonyl, benzyloxycarbonyl, paramethoxybenzyloxycarbonyl, paranitrobenzyloxycarbonyl or benzyl, Q^{2b} represents a single bond, a linear or branched C_{1-6} alkylene, a linear or branched C_{2-6} alkenylene, a linear or branched C_{2-6} alkynylene or a group of the following formula:

[0325]

[Chemical formula 42]



(which has the same meaning as described above) and m_1 stands for an integer of 1 to 6].

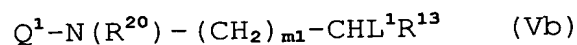
[0326]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) forms an amide bond, the compound of the formula (Ib) can be synthesized by alkylating the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) with any one of the compounds represented by the following formulas (Va) to (Vd):

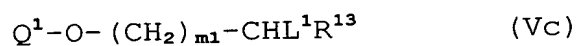
[0327]



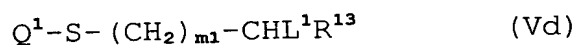
[0328]



[0329]



[0330]



[0331]

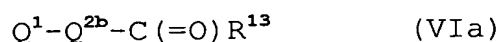
[wherein Q^1 , Q^{2b} , R^{13} , R^{20} and m_1 have the same meanings as described above, and L^1 represents an eliminating group frequently used in the organic chemistry, such as chlorine, bromine, iodine, methylsulfonyloxy or paratoluenesulfonyloxy].

[0332]

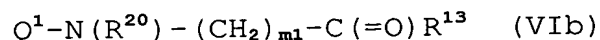
When the nitrogen atom of Q^{3b} of the compound represented

by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can be prepared by reductive alkylation, that is, by forming the corresponding imine with a carbonyl compound represented by any one of the following formulas (VIa) to (VIId):

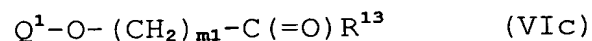
[0333]



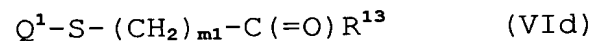
[0334]



[0335]



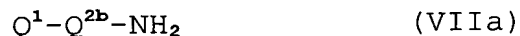
[0336]



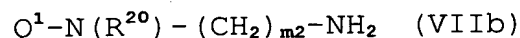
[0337]

[wherein Q^1 , Q^{2b} , R^{13} , R^{20} and $m1$ have the same meanings as described above], followed by reduction; by reacting the compound of the formula (IIIa) with a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole and a compound containing a primary amine represented by any one of the following formulas (VIIa) to (VIId):

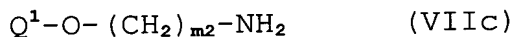
[0338]



[0339]



[0340]



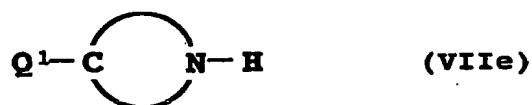
[0341]



[0342]

[0343]

[Chemical formula 43]



wherein Q^1 , Q^{2b} and R^{20} have the same meanings as described above and m_2 stands for an integer of 2 to 6 and a group of the following formula:

[0344]

[Chemical formula 44]



represents a 5- or 6-membered heterocyclic group which may have a substituent)], thereby forming the corresponding urea derivative; or by reacting the amine of the formula (IIIa) with an isocyanate derivative or an isocyanate prepared from a carboxylic acid represented by any one of the formulas (IVa) to (IVd).

[0345]

When in the structure of Q^1 of the compound represented by the formula (Ib), a halogen- or

trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, coupling reaction can be effected with a boric-acid-substituted aryl compound in the presence of a transition metal catalyst.

[0346]

When in the structure of Q^1 of the compound represented by the formula (Ib), an alkenyl group or boric-acid-substituted alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group in the presence of a transition metal catalyst.

[0347]

When in the structure of Q^1 of the compound represented by the formula (Ib), a boric-acid-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl compound or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl compound. When in the structure of Q^1 of the compound represented by the formula (Ib), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group is contained, it can be subjected to coupling reaction with an alkenyl compound in the presence of a transition metal catalyst, whereby the compound of the formula (Ib) can be obtained. If the nitrogen atom of Q^{3b} of the compound (Ib) so obtained has been protected, the compound of the formula (Ia) can be obtained

by deprotection as needed.

[0348]

Examples of the carboxylic acids of the following formulas (IVa) to (IVd) in an activated form include acid mixed acid anhydrides available by reacting any one of the carboxylic acids of the formulas (IVa) to (IVd) with a chloroformate ester such as isobutyl chloroformate; acid halides such as acyl chloride prepared using an acid halide such thionyl chloride; active esters obtained by reacting with a phenol such as paranitrophenol or pentafluorophenyl-trifluoroacetate; active esters obtained by reacting with N-hydroxybenztriazole or N-hydroxysuccinimide; reaction products with 1-benzotriazolyloxy-(pyrrolidino)-phosphonium hexafluorophosphate, N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride which is usually employed for the peptide synthesis of amino acid, reaction products with diethyl cyanophosphonate (salting-in method) and reaction products with triphenylphosphine and 2,2'-dipyridylsulfide (Mukaiyama's method).

[0349]

The resulting carboxylic acid in an activated form is then reacted with the compound of the formula (IIIa) or salt thereof generally in the presence of an appropriate base in an inert solvent at -78°C to 150°C, whereby the compound of the formula (Ib) can be obtained.

[0350]

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium methoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0351]

Examples of the inert solvent include alkyl halide solvents such as dichloromethane, chloroform and carbon tetrachloride; ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane; aromatic solvents such as benzene and toluene; and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. In addition to them, sulfoxide solvents such as dimethylsulfoxide and sulfolane and ketone solvents such as acetone and methyl ethyl ketone can be used if they are suited.

[0352]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) forms an amide bond, the alkylation of

the nitrogen atom is carried out by reacting the compound (IIIa) with the compound represented by any one of the formulas (Va) to (Vd) in the presence of an appropriate base in an inert solvent at -78 to 150°C, whereby the compound of the formula (Ib) can be obtained. Specific examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU).

[0353]

Examples of the inert solvent include ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane and amide solvents such as N,N-dimethylformamide.

[0354]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can be obtained by reacting the compound of the formula (IIIa) with the carbonyl compound of any one of the formulas (VIa) to (VIId) to form the corresponding imine, generally in an inert solvent, if necessary in the presence of an organic acid such as acetic acid, a mineral acid such as hydrochloric acid or a Lewis acid such as aluminum chloride at -20 to 150°C; and then hydrogenating

the resulting imine in an inert solvent in the presence of a boron hydride reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxymborohydride or a catalytic reduction catalyst such as palladium-carbon catalyst at 10 to 110°C.

[0355]

Preferred examples of the inert solvent include carbon halides such as dichloromethane, chloroform and carbon tetrachloride, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane, benzene solvents such as toluene and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one.

[0356]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the reaction product of the compound of any one of the formulas (VIIa) to (VIId) containing a primary amine or the compound of the formula (VIIe) containing a secondary amine with a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole can be acted on the compound of the formula (IIIa) to introduce it to the corresponding urea derivative. The derivative can be synthesized by reacting the primary amine compound of any one of the formulas (VIIa) to (VIId) or the secondary amine compound of the formula (VIIe) and the compound of the formula (IIIa) with a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole, successively in this order if necessary

in the presence of a base, in an inert solvent.

[0357]

Examples of the inert solvent include halogen solvents such as dichloromethane, chloroform and carbon tetrachloride; ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane; benzene solvents such as toluene; and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. Among them, dichloromethane, tetrahydrofuran and toluene are preferred.

[0358]

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is effected within a temperature range of from -70°C to 110°C.

[0359]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can also be obtained by reacting the compound of the formula (IIIa) with an isocyanate derivative in an inert solvent at -20 to 100°C.

[0360]

The isocyanate derivative can be synthesized by converting the carboxylic acid of the formula (IVa) into the corresponding acid halide by using an acid halide such as thionyl chloride or oxalyl chloride in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C , reacting the resulting acid halide with sodium azide in an inert solvent such as tetrahydrofuran, chloroform or toluene at a temperature range of from 0 to 80°C , and then heating the reaction mixture at 20 to 100°C ; by reacting the carboxylic acid of the formula (IVa) with a chloroformate such as isobutyl chloroformate in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C to obtain the corresponding mixed acid anhydride, reacting the mixed acid anhydride with sodium azide within a temperature range of from 0 to 80°C and then heating the reaction mixture at 20 to 100°C ; or by introducing the carboxylic acid of the formula (IVa) into the corresponding hydrazide through an ester in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C , reacting the hydrazide with nitric acid or alkyl ester thereof to convert it into the corresponding acyl azide and then heating the resulting acyl azide in a solvent such as chloroform, dichloroethane, toluene, xylene or N,N-dimethylformamide at 20 to 150°C .

[0361]

The compound of the formula (Ib) can also be prepared by reacting the carboxylic acid of the formula (IVa) with diphenylphosphoryl azide in the presence of a base such as

triethylamine, in an inert solvent such as chloroform, tetrahydrofuran, toluene or N,N-dimethylformamide at a temperature range of 10 to 140°C and then reacting the reaction mixture with the amine of the formula (IIIa).

[0362]

When in the structure of Q^1 of the compound represented by the formula (Ib), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, the compound can be subjected to coupling reaction with a boric-acid-substituted aryl derivative by using a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (0), in a two-phase solvent such as benzene-water or toluene-water, amide solvent such as N,N-dimethylformamide or ether solvent such as tetrahydrofuran or dimethoxyethane, if necessary in the presence of sodium carbonate, sodium hydroxide, calcium hydroxide, barium hydroxide, potassium phosphate or cesium carbonate at a temperature range of 20 to 150°C for 0.5 to 120 hours.

[0363]

When an alkenyl group or boric-acid-substituted alkenyl group is contained in the structure of Q^1 of the compound represented by the formula (Ib), coupling reaction of the compound with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group can be effected using a transition metal

catalyst such as palladium acetate, if necessary in the presence of an appropriate base or cesium fluoride, in an amide solvent such as N,N-dimethylformamide, at a temperature range of 20 to 150°C for 0.5 to 120 hours. When a boric-acid-substituted aryl group is contained in the structure of Q^1 of the compound represented by the formula (Ib), coupling reaction of the compound with a halogen- or trifluoromethanesulfonyloxy-substituted aryl derivative or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl derivative can be effected. When a halogen- or trifluoromethanesulfonyloxy-substituted aryl group is contained in the structure of Q^1 of the compound, coupling reaction of the compound with an alkenyl compound can be effected using a transition metal catalyst, whereby the compound of the formula (Ib) can be obtained.

[0364]

If the nitrogen atom of Q^{3b} of the resulting compound represented by the formula (Ib) has been protected, the compound of the formula (Ia) can be obtained by deprotection as needed.

[0365]

<Synthesis of the compound represented by the formula (IIa)>

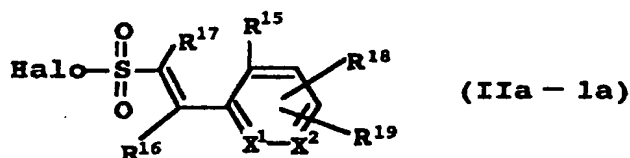
The sulfonic acid halide of the formula (IIa) can be synthesized in a known manner or by application thereof. The ordinarily employed synthesis process will be described below.

[0366]

Among the sulfonic acid halides represented by the formula (IIa), a sulfonic acid halide represented by the following formula (IIa-1a):

[0367]

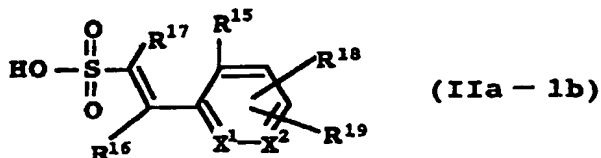
[Chemical formula 45]



[wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , X^1 , X^2 and Halo have the same meanings as described above] can be synthesized by any one of the various processes reported to date (The Chemistry of Sulfonic Acids Esters and their Derivatives, Edited by S. Patai and Z. Rappoport, 1991, John Wiley & Sons Ltd.), for example, halogenation of a sulfonic acid of the following formula (IIa-Ib):

[0368]

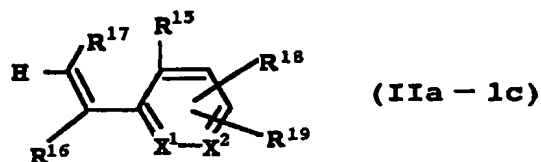
[Chemical formula 46]



[wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , X^1 and X^2 have the same meanings as described above] or chlorosulfonylation of the unsaturated bond represented by the following formula (IIa-1c):

[0369]

[Chemical formula 47]



[wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , X^1 and X^2 have the same meanings as described above].

[0370]

For example, the sulfonic acid halide of the formula (IIa-Ia) can be obtained by reacting the sulfonic acid of the formula (IIa-Ib) with a thionyl halide in the presence of N,N-dimethylformamide at 0 to 150°C for 0.5 to 24 hours. At this time, the reaction system may be diluted with an inert solvent such as dichloromethane, chloroform, carbon tetrachloride, N-methylpyrrolidin-2-one, dimethylsulfoxide or sulfolane.

[0371]

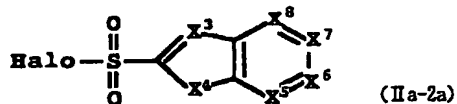
The sulfonic acid halide of the formula (IIa-Ia) can be obtained by reacting the unsaturated-bond-containing compound of the formula (IIa-Ic) with a thionyl halide or chlorosulfonic acid in an inert solvent such as N,N-dimethylformamide at 0 to 150°C for 0.5 to 24 hours.

[0372]

Among the sulfonic acid halides represented by the formula (IIa), a sulfonic acid halide represented by the following formula (IIa-2a):

[0373]

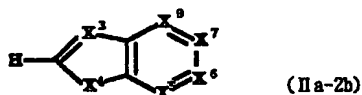
[Chemical formula 48]



[wherein X³, X⁴, X⁵, X⁶, X⁷, X⁸ and Halo have the same meanings as described above] can be obtained by the processes so far reported (Japanese Patent Application Laid-Open No. Sho 60-204760, Japanese Patent Application Laid-Open No. Sho 62-116575, Japanese Patent Application Laid-Open No. Hei 4-128266) or by application thereof, for example, by reacting the fused heterocycle represented by the following formula (IIa-2b):

[0374]

[Chemical formula 49]



[wherein X³, X⁴, X⁵, X⁶, X⁷ and X⁸ have the same meanings as described above] with a base and then with sulfur dioxide and then reacting the reaction mixture with a halogenating agent.

[0375]

The compound of the formula (IIa-2b) is obtained, for example, by reacting the fused heterocycle of the formula (IIa-2b) with an appropriate base in an ether-type inert solvent at -78°C to 0°C, reacting the reaction mixture with sulfur dioxide at -78°C to 0°C, and then reacting with a halogenating agent in an alkyl halide type inert solvent at -50°C to 50°C.

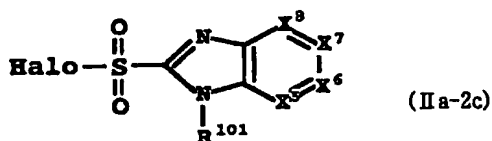
Specific examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and t-butyl lithium, dialkylaminolithium such as lithium diisopropylamide; organometallic bases of bisilylamine such as lithium bis(trimethylsilyl)amide. Examples of the ether-type inert solvent include diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and dioxane. Preferred examples of the halogenating agent include chlorine, bromine, phosphorus pentachloride, thionyl chloride, N-chlorosuccinimide and N-bromosuccinimide, while those of the alkyl halide type inert solvent include dichloromethane, chloroform and tetrachloroethane.

[0376]

Among the compounds represented by the formula (IIa-2a), the corresponding sulfonyl chloride of the compound represented by the following formula (IIa-2c):

[0377]

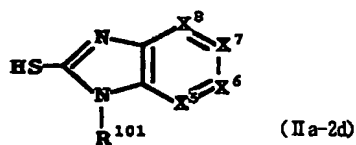
[Chemical formula 50]



[wherein R^{101} , X^5 , X^6 , X^7 , X^8 and Halo have the same meanings as described above] can be obtained by reacting the compound of the following formula (IIa-2d):

[0378]

[Chemical formula 51]



[wherein R^{101} , X^5 , X^6 , X^7 and X^8 have the same meanings as described above] with halogen such as a chlorine gas at 0 to 30°C for 10 minutes to 6 hours in water or a mixed solvent of water with an organic carboxylic acid such as acetic acid.

[0379]

The reaction between the compound of the formula (IIa-2d) and halogen is carried out at 0 to 20°C usually in water or a 10 to 90% aqueous solution of acetic acid if necessary in the presence of a Lewis acid such as ferric chloride as a catalyst.

[0380]

<Reaction of a compound of the formula (Ia) with a compound of the formula (IIa)>

The compound of the formula (I) can be obtained generally by reacting the compound of the formula (Ia), which has been synthesized by the above-described process or the like, with the sulfonic acid halide of the formula (IIa) which has been synthesized by the above-described process or the like, in the presence of an appropriate base in an inert solvent at -78 to 150°C.

[0381]

The resulting compound of the formula (I) can be subjected to deprotection or chemical conversion of a substituent as needed.

[0382]

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium methoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0383]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane and mixed solvents thereof.

[0384]

[Preparation Process-1-(1)]

When the nitrogen atom of Q^{3a} of the compound represented

by the formula (Ia), which is to be sulfonylated, exists as a primary or secondary amine, preferred examples of the base include carbonates and hydroxides of an alkali metal or an alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) and usable examples of the solvent include, in addition to inert solvents, water, alcohol solvents such as ethanol and butanol and ester solvents such as ethyl acetate.

[0385]

[Preparation Process-1-(2)]

When the nitrogen atom of Q^{3a} of the compound represented by the formula (Ia), which is to be sulfonylated, forms an amide group, preferred examples of the base include alkoxides and hydrides of an alkali metal or an alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU). Examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane, dioxane and N,N-dimethylformamide.

[0386]

[Preparation Process-2]

A process for preparing the sulfonyl derivative (I) by acylating the nitrogen atom of Q^{3a} of the compound represented by the formula (VIIIa):



[wherein Q^{3a} and Q^4 have the same meanings as described above] with any one of the carboxylic acids represented by the formulas (IVa) to (IVd):

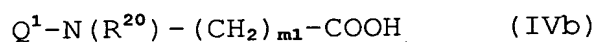
[0387]



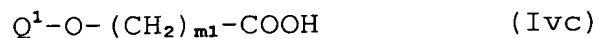
[0388]



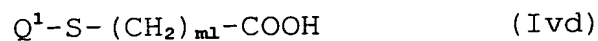
[0389]



[0390]



[0391]



[wherein Q^1 , Q^2 , Q^{2b} , Q^4 , R^{20} and $m1$ have the same meanings as described above] or the activated form thereof which are available by the process reported to date or the chemically usual process.

[0392]

The compound represented by the formula (VIIIa) can be

synthesized in various processes. Some of them will next be described.

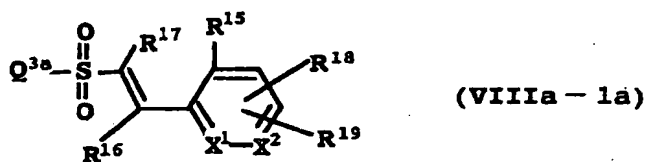
<<Synthesizing process of a compound represented by the formula (VIIIa)>>

<<Synthesizing process of a compound represented by the formula (VIIIa-Ia)>>

Among the compounds represented by the formula (VIIIa), the compound of the formula (VIIIa-Ia):

[0393]

[Chemical formula 52]



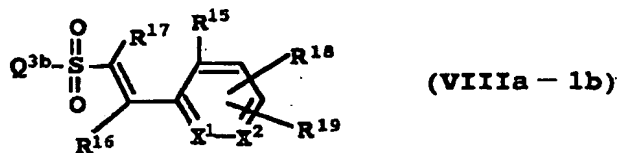
[wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , X^1 , X^2 and Q^{3a} have the same meanings as described above] can be synthesized as described below.

[0394]

The compound of the following formula (VIIIa-Ib):

[0395]

[Chemical formula 54]



[wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , X^1 , X^2 and Q^{3b} have the same meanings as described above] can be obtained by sulfonylating the nitrogen atom of the primary amine, secondary amine or amide

of the compound of the formula (IIIa):

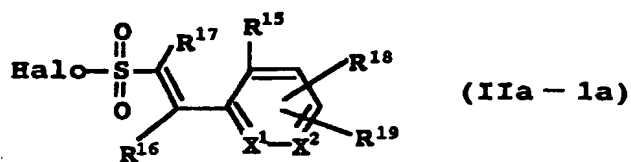
[0396]



[wherein Q^{3b} has the same meaning as described above] with a compound represented by the following formula (IIa-1a):

[0397]

[Chemical formula 53]



[wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , X^1 , X^2 and Halo have the same meanings as described above] in the presence of an appropriate base in an inert solvent at -78 to 150°C .

[0398]

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium botoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and

diazabicyclo[5.4.0]undec-7-ene (DBU).

[0399]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide, sulfolane and acetone.

[0400]

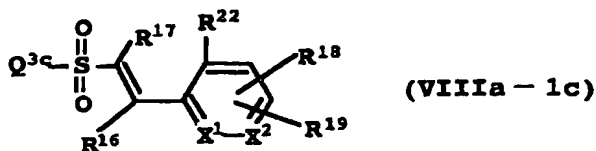
If the nitrogen atom of Q^{3b} of the resulting compound represented by the formula (VIIIa-1b) has been protected, the compound of the formula (VIIIa-1a) can be obtained by deprotection as needed.

[0401]

The compound of the formula (VIIIa-1a) can be obtained by removing, in an appropriate manner, the protecting group from the nitrogen atom of the compound represented by the following formula (VIIIa-1c):

[0402]

[Chemical formula 55]



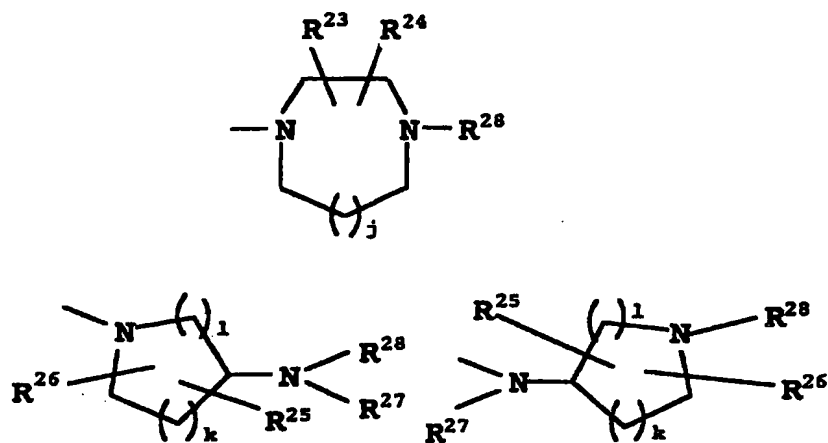
[wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , X^1 and X^2 have the same meanings as described above, R^{22} represents

a hydrogen atom,

an alkyl group,
 a hydroxyl group protected with a methoxymethyl,
 tetrahydropyranyl or the like group,
 a hydroxyalkyl group having a hydroxyl group protected
 with a methoxymethyl, tetrahydropyranyl or the like group,
 an alkoxyl group,
 an alkoxyalkyl group,
 a dialkoxyalkyl group,
 a dialkylamino group,
 a monoalkylamino group having an amino group protected
 with a tertiary butoxycarbonyl group,
 a dialkylaminoalkyl group,
 a monoalkylaminoalkyl group having an amino group
 protected with a tertiary butoxycarbonyl group,
 a dialkylaminocarbonyl group,
 a dialkylaminocarbonylalkyl group,
 a dialkylaminoalkyloxy group,
 a monoalkylaminoalkyloxy group having an amino group
 protected with a tertiary butoxycarbonyl group,
 a dialkylaminocarbonylalkyloxy group or the like; and Q^{3c}
 represents any one of the following groups:

[0403]

[Chemical formula 56]



(wherein when the carbon atom to which R^{23} , R^{24} , R^{25} or R^{26} has been bonded is not adjacent to the nitrogen atom, R^{23} , R^{24} , R^{25} and R^{26} each independently represents:

- a hydrogen atom,
- an alkyl group,
- a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,
- a hydroxyalkyl group having a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,
- an alkoxy group,
- an alkoxyalkyl group,
- a dialkoxyalkyl group,
- a dialkylamino group,
- a monoalkylamino group having an amino group protected with a tertiary butoxycarbonyl group,
- a dialkylaminoalkyl group,
- a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,
 a dialkylaminocarbonylalkyl group,
 a dialkylaminoalkyloxy group,
 a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,
 a dialkylaminocarbonylalkyloxy group or the like; and when the carbon atom to which R^{23} , R^{24} , R^{25} or R^{26} has been bonded is adjacent to the nitrogen atom, R^{23} , R^{24} , R^{25} and R^{26} each independently represents:

a hydrogen atom,
 an alkyl group,
 a hydroxyalkyl group having a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,
 an alkoxyalkyl group,
 a dialkoxyalkyl group,
 a dialkylaminoalkyl group,
 a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,
 a dialkylaminocarbonyl group,
 a dialkylaminocarbonylalkyl group,
 a dialkylaminoalkyloxy group or the like.

[0404]

R^{25} and R^{26} , as well as R^{23} and R^{24} , may be coupled together to form a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may

have a substituent.

[0405]

R^{27} represents:

an alkyl group,

a hydroxyalkyl group having the hydroxyl group protected,

a hydroxyalkylcarbonyl group having the hydroxyl group protected,

a hydroxyalkylsulfonyl group having the hydroxyl group protected,

an alkoxyalkyl group,

an alkoxyalkylcarbonyl group,

an alkoxyalkylsulfonyl group,

an alkylcarbonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonyl group,

an alkylsulfonylalkyl group,

an alkoxy carbonyl group,

an alkoxy carbonylalkyl group,

an alkoxy carbonylalkylcarbonyl group,

an alkoxy carbonylalkylsulfonyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having the amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group, or the like.

R^{26} and R^{27} , or R^{25} and R^{27} may be coupled together to form a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent.

[0406]

R^{28} represents a tertiary butoxycarbonyl, benzyl or triphenylmethyl group which means a protecting group of the nitrogen atom, j and k each independently represents an integer of 0 or 1 and l stands for an integer of 1 to 3 with the proviso that the sum of k and l stands for an integer of 1 to 4.)]

[0407]

The compound represented by the formula (VIIIa-1c) can be obtained by reacting an amino compound which is available by the known process or application thereof and is represented by the following formula (IIIb):

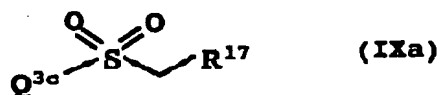
[0408]



[wherein Q^{3c} has the same meaning as described above] with an alkylsulfonic acid halide in the presence of an appropriate base; reacting the resulting sulfonamide represented by the following formula (IXa):

[0409]

[Chemical formula 57]

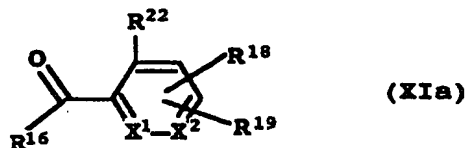


[wherein R^{17} and Q^{3c} have the same meanings as described above]

with a carbonyl compound represented by the following formula (XIa):

[0410]

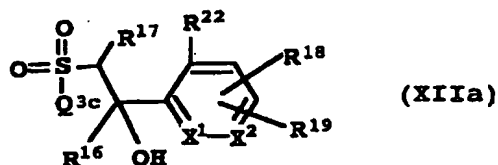
[Chemical formula 58]



[wherein R^{16} , R^{18} , R^{19} , R^{22} , X^1 and X^2 have the same meanings as described above] in an inert solvent in the presence of an appropriate base to obtain the corresponding alcohol product represented by the following formula (XIIa):

[0411]

[Chemical formula 59]



[wherein R^{16} , R^{17} , R^{18} , R^{19} , R^{22} , Q^{3c} , X^1 and X^2 have the same meanings as described above]; converting the alcohol moiety of the alcohol product (XIIa) into a methanesulfonyloxy group or the like in the presence of an appropriate base, or converting the alcohol moiety into a halogen atom by using a phosphorus halide or triphenylphosphine/carbon tetrahalide, thereby forming an eliminating group; and then eliminating methanesulfonic acid or hydrogen halide in the presence of an appropriate base.

[0412]

The sulfonamide compound of the formula (IXa) can be obtained by reacting the amino compound of the formula (IIb), which is available in a known process or by application thereof, with an alkylsulfonic halide which may have a substituent, in the presence of an appropriate base, in an inert solvent at -78 to 150°C.

[0413]

Examples of the base include carbonates of an alkali metal or alkaline earth metal, such as sodium carbonate and potassium carbonate and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0414]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. Dimethylsulfoxide, sulfolane, acetone or the like can be used, though depending on the kind of the base employed.

[0415]

The alcohol compound of the formula (XIIa) can be obtained by reacting the sulfonamide of the formula (IXa) with a carbonyl compound of the formula (XIa) in the presence of an appropriate base in an inert solvent at -78 to 110°C.

[0416]

Examples of the base include hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and bisilylamine such as lithium bis(trimethylsilylamide); organometallic bases typified by dialkylaminolithium such as lithium diisopropylamide. Examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane and dioxane.

[0417]

The compound of the formula (VIIIa-1c) can be obtained by treating the hydroxyl group of the alcohol product of the formula (XIIa) with a phosphorus halide such as phosphorus pentachloride or a triphenylphosphine-halogen complex such as triphenylphosphine dibromide at -20 to 110°C, if necessary in the presence of an appropriate base, for example, the carbonate of an alkali metal or alkaline earth metal, such as sodium carbonate or potassium carbonate, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo[5.4.0]undec-7-ene (DBU), in a solvent such as dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene or N,N-dimethylformamide, thereby obtaining the corresponding halide, and then eliminating the hydrogen halide from the resulting halide under basic conditions, for example, by

treating at -78 to 150°C with a carbonate, alkoxide, hydroxide or hydride of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, an organometallic base such as alkyl lithium, e.g., n-butyl lithium or dialkylamine, e.g., lithiumbis(trimethylsilyl)amide, an organometallic base typified by dialkylaminolithium such as lithium diisopropylamide, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

[0418]

The compound of the formula (VIIIa-1c) can also be obtained by treating the hydroxyl group of the alcohol product represented by the formula (XIIa) with an alkyl- or arylsulfonic acid chloride such as methanesulfonic acid chloride in the presence of an appropriate base, for example, a carbonate of an alkali metal or alkaline earth metal such as sodium carbonate or potassium carbonate or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or

diazabicyclo[5.4.0]undec-7-ene (DBU), in a solvent such as dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene or N,N-dimethylformamide at -20 to 110°C to obtain the corresponding alkyl- or arylsulfonate derivative; and then eliminating the alkyl- or arylsulfonic acid from the resulting alkyl- or arylsulfonate derivative under basic conditions.

[0419]

Described specifically, the compound of the formula (VIIIa-1c) can be obtained by treating the resulting alkyl- or arylsulfonate derivative at -78 to 150°C in the presence of a carbonate, alkoxide, hydroxide or hydride of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, an organometallic base such as alkyl lithium, e.g., n-butyl lithium or bisilylamine, e.g., lithium bis(trimethylsilyl)amide, an organometallic base typified by dialkylaminolithium such as lithium isopropylamide, a bisilylamine base organometallic compound such as lithium bis(trimethylsilyl)amide, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide,

N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

[0420]

The compound of the formula (VIIIa-1c) can also be obtained by treating the sulfonamide of the formula (IXa) with a silyl halide such as trimethylsilyl chloride in the presence of an appropriate base in an inert solvent to convert it to the corresponding silyl compound, reacting the resulting silyl compound with a carbonyl compound of the formula (XIa) in the presence of a base in an inert solvent and then treating the reaction product under acidic to basic aqueous conditions (Peterson's reaction).

[0421]

Described specifically, the compound of the formula (VIIIa-1c) can be obtained by treating the sulfonamide of the formula (IXa) with an alkylsilyl chloride such as trimethylsilyl chloride at -78 to 110°C in the presence of a hydride of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride or potassium hydride, an organometallic base such as alkyl lithium, e.g., n-butyl lithium or bisilylamine, e.g., lithium bis(trimethylsilyl)amide or an organometallic base typified by dialkylaminolithium such as lithium bis(trimethylsilyl)amide, for example, in a solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, to convert it to the corresponding silyl compound, condensing with the carbonyl compound of the

formula (XIa) under the same conditions and then treating the condensate under acidic to basic aqueous conditions.

[0422]

The protecting group of the nitrogen atom of the compound represented by the formula (VIIIa-1c) can be removed by the ordinarily employed process. Described specifically, when the protecting group is a tertiary butoxycarbonyl group, it can be removed by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. It can also be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIIIa-1c) can be obtained.

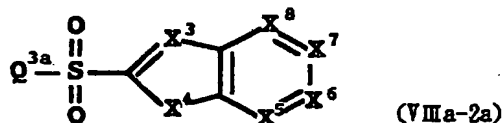
[0423]

<Synthesis of the compound represented by the formula (VIIIa-2a)>

Among the compounds represented by the formula (VIIIa),
the compound of the formula (VIIIa-2a):

[0424]

[Chemical formula 60]



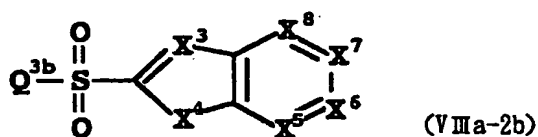
[wherein X^3 , X^4 , X^5 , X^6 , X^7 , X^8 and Q^{3a} have the same meanings as described above] can be synthesized by the following process.

[0425]

Described specifically, the compound of the following
formula (VIIIa-2b):

[0426]

[Chemical formula 62]



[wherein X^3 , X^4 , X^5 , X^6 , X^7 , X^8 and Q^{3b} have the same meanings as described above] can be obtained by sulfonylating the nitrogen atom of the primary or secondary amine or amide of the compound of the formula (IIIa):

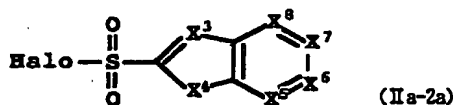
[0427]



[wherein Q^{3b} has the same meaning as described above] with a sulfonic acid halide represented by the following formula (IIa-2a):

[0428]

[Chemical formula 61]



[wherein X³, X⁴, X⁵, X⁶, X⁷, X⁸ and Halo have the same meanings as described above] in the presence of an appropriate base in an inert solvent at -78 to 150°C.

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as bisilylamine, e.g., lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0429]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide, sulfolane and acetone.

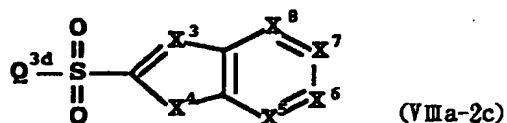
[0430]

When the nitrogen atom of Q^{3b} of the resulting compound represented by the formula (VIIIa-2b) has been protected, the compound of the formula (VIIIa-2a) can be obtained by carrying out deprotection as needed.

Alternatively, the compound of the formula (VIIIa-2a) can be obtained by removing, as needed in an appropriate manner, the protecting group of the nitrogen atom of Q^{3d} of the compound which is available by the below-described preparation process and is represented by the following formula (VIIIa-2c):

[0431]

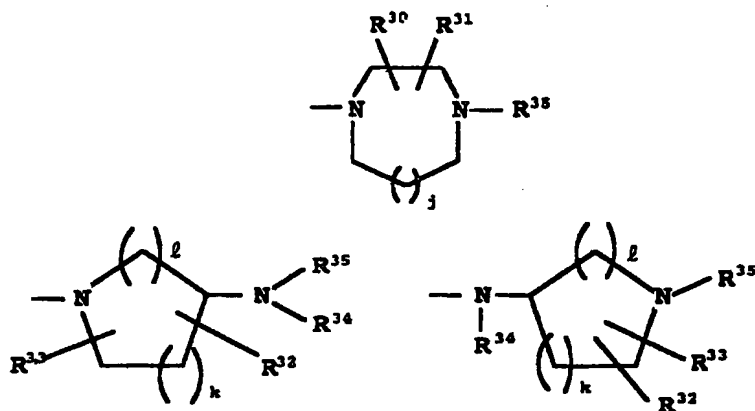
[Chemical formula 63]



[Wherein X^3 , X^4 , X^5 , X^6 , X^7 and X^8 have the same meanings as described above and Q^{3d} means any one of the following groups:

[0432]

[Chemical formula 64]



(wherein, when the carbon atom to which each of R^{30} , R^{31} , R^{32} and R^{33} has been bonded is not adjacent to a nitrogen atom, R^{30} , R^{31} , R^{32} and R^{33} each independently represents

- a hydrogen atom,
- an alkyl group,
- a hydroxyl group,
- a hydroxyl group protected with a methoxymethyl or tetrahydropyranyl or the like group,
- a hydroxyalkyl group,
- a hydroxyalkyl group having a hydroxyl group protected with a methoxymethyl or tetrahydropyranyl or the like group,
- an alkoxyl group,
- an alkoxyalkyl group,
- a dialkoxyalkyl group,
- a dialkylamino group,
- a monoalkylamino group having an amino group protected with a tertiary butoxycarbonyl group,
- a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

a dialkylaminoalkyloxy group,

a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a monoalkylaminocarbonylalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonylalkyloxy group,

a dialkylaminoalkyloxy group,

a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a carbamoyl group,

a monoalkylcarbamoyl group,

a dialkylcarbamoyl group,

a carbamoylalkyl group,

a monoalkylcarbamoylalkyl group,

a dialkylcarbamoylalkyl group,

a pyrrolidinocarbonyl group,

a pyrrolidinocarbonylalkyl group,

a piperidinocarbonyl group,

a piperidinocarbonylalkyl group,

a morpholinocarbonyl group,

a morpholinocarbonylalkyl group,

a dialkylaminocarbonylalkyloxy group, or the like;

[0433]

when the carbon atom to which each of R^{30} , R^{31} , R^{32} and R^{33} has been bonded is adjacent to a nitrogen atom, R^{30} , R^{31} , R^{32} and R^{33} each independently represents

- a hydrogen atom,
- an alkyl group,
- a hydroxyalkyl group having a hydroxy group protected with a methoxymethyl, tetrahydropyranyl or the like group,
- an alkoxyalkyl group,
- a dialkoxyalkyl group,
- a dialkylaminoalkyl group,
- a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,
- a dialkylaminocarbonyl group,
- a dialkylaminocarbonylalkyl group,
- a carbamoyl group,
- a monoalkylcarbamoyl group,
- a carbamoylalkyl group,
- a monoalkylcarbamoylalkyl group,
- a pyrrolidinocarbonyl group,
- a pyrrolidinocarbonylalkyl group,
- a piperidinocarbonyl group,
- a piperidinocarbonylalkyl group,
- a morpholinocarbonyl group,

a morpholinocarbonylalkyl group,

a dialkylaminoalkyloxyalkyl group or the like;

[0434]

R^{30} and R^{31} , or R^{32} and R^{33} may be coupled together to form a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent;

R^{34} represents

an alkyl group,

a hydroxyalkyl group having a protected hydroxyl group,

a hydroxyalkylcarbonyl group having a protected hydroxyl group,

a hydroxyalkylsulfonyl group having a protected hydroxyl group,

an alkoxyalkyl group,

an alkoxyalkylcarbonyl group,

an alkoxyalkylsulfonyl group,

an alkylcarbonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonyl group,

an alkylsulfonylalkyl group,

an alkoxy carbonyl group,

an alkoxy carbonylalkyl group,

an alkoxy carbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,
 a dialkylaminoalkyl group,
 a monoalkylaminoalkyl group having an amino group
 protected with a tertiary butoxycarbonyl group,
 a dialkylaminocarbonyl group,
 a dialkylaminocarbonylalkyl group or the like;

R^{32} and R^{34} , or R^{33} and R^{34} may be coupled together to form
 a saturated or unsaturated 5- to 7-membered heterocyclic group
 which may have a substituent;

[0435]

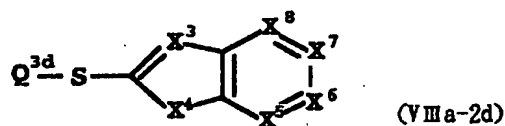
R^{35} represents an ordinarily employed protecting group for
 a nitrogen atom such as tertiary butoxycarbonyl group, benzyl
 group or triphenylmethyl group; j and k independently
 represents 0 or an integer of 1; and l stands for an integer
 of 1 to 3 with the proviso that the sum of k and l stands for
 an integer of 1 to 4)].

[0436]

The compound represented by the following formula
 (VIIIa-2d):

[0437]

[Chemical formula 66]



[wherein X^3 , X^4 , X^5 , X^6 , X^7 , X^8 and Q^{3d} have the same meanings as
 described above] can be obtained by reacting an amino compound,

which is available in a known manner or by application thereof and is represented by the following formula (IIIc):

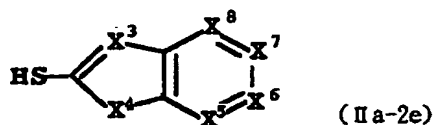
[0438]



[wherein Q^{3d} has the same meaning as described above] with a fused heterocyclic thiol compound represented by the following formula (IIa-2e):

[0439]

[Chemical formula 65]



[wherein X^3 , X^4 , X^5 , X^6 , X^7 and X^8 have the same meanings as described above] in the presence of an appropriate base and oxidizing agent.

[0440]

The compound of the formula (VIIIa-2c) can be obtained by oxidizing the resulting compound of the formula (VIIIa-2d) in an inert solvent in the presence of an appropriate base.

[0441]

The compound of the formula (VIIIa-2d) can be obtained by reacting an amino compound, which is represented by the formula (IIIc) and is available in a known manner or by application thereof, with a thiol represented by the formula (IIa-2e) at -10 to 50°C in the presence of an appropriate base and oxidizing agent in water, an alcohol or dioxane or a mixed solvent thereof.

[0442]

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide. Examples of the oxidizing agent include oxygen, chlorine, bromine, iodine and hypochlorous acid. The compound of the formula (VIIIa-2c) can be obtained by reacting the resulting compound of the formula (VIIIa-2d) with an inorganic oxidizing agent such as potassium permanganate or hydrogen peroxide or an organic oxidizing agent such as 3-chloroperbenzoic acid at -30°C to 60°C in the presence of an appropriate base in water, alcohol or a mixed solvent thereof.

[0443]

The protecting group of the nitrogen atom can be removed from the compound of the formula (VIIIa-2c) by an ordinarily employed process. Described specifically, when the nitrogen atom has been protected with a tertiary butoxycarbonyl group, the protecting group can be removed using an appropriate acid, for example, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid,

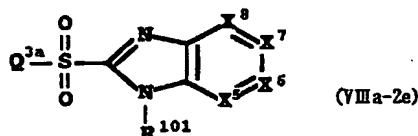
trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium or by hydrogenolysis in the presence of a palladium-carbon catalyst. By deprotection as described above, the compound represented by the formula (VIIIa-2a) can be obtained.

[0444]

Among the compounds represented by the formula (VIIIa-2a), the compound of the following formula (VIIIa-2e):

[0445]

[Chemical formula 67]



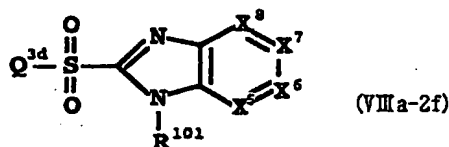
[wherein X^3 , X^4 , X^5 , X^6 , X^7 , X^8 , R^{101} and Q^{3a} have the same meanings as described above] can also be obtained by removing the protecting group from the nitrogen atom of Q^{3a} of the compound which is available by the below-described preparation process and is represented by the formula (VIIIa-2f).

[0446]

Described specifically, the compound of the following formula (VIIIa-2f):

[0447]

[Chemical formula 69]



[wherein X^3 , X^4 , X^5 , X^6 , X^7 , X^8 , R^{101} and Q^{3d} have the same meanings as described above] can be obtained by reacting an amino compound which is available in a known manner or by the application thereof and is represented by the following formula (IIIc):

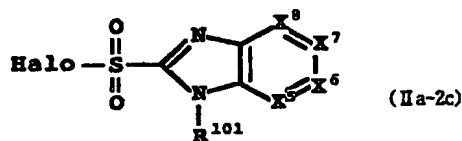
[0448]



[wherein Q^{3d} has the same meaning as described above] with an acid halide represented by the following formula (IIa-2c):

[0449]

[Chemical formula 68]



[wherein X^3 , X^4 , X^5 , X^6 , X^7 , X^8 , R^{101} and Halo have the same meanings as described above].

[0450]

The compound of the formula (VIIIa-2f) can be obtained by reacting the compound of the formula (IIa-2d) with halogen such as chlorine gas at 0 to 30°C for 10 minutes to 6 hours in water or a mixed solvent of water with an organic carboxylic acid such as acetic acid, thereby forming the corresponding sulfonyl chloride; and then adding the resulting sulfonyl chloride to an amino compound of the formula (IIIc), which has been dissolved

in an appropriate solvent, at -50 to 40°C.

[0451]

The reaction between the compound of the formula (IIa-2d) and halogen is carried out at 0 to 20°C, usually in water or a 10 to 90% aqueous solution of acetic acid, if necessary in the presence of a Lewis acid such as ferric chloride as a catalyst. As the halogen, a chlorine gas is used. The reaction of the resulting acid chloride (IIa-2c) with the amine of the formula (IIIc) is carried out at -20 to 50°C in a solvent, for example, water, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform or acetone or a mixed solvent thereof, if necessary in the presence of a base, whereby the compound of the formula (VIIIa-2f) can be obtained. Specific examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0452]

The protecting group of the nitrogen atom of the compound represented by the formula (VIIIa-2f) can be removed by the ordinarily employed process. Described specifically, when the

protecting group is a tertiary butoxycarbonyl group, it can be removed by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl group can be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIIIa-2e) can be obtained.

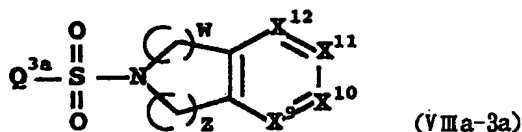
[0453]

<Synthesis of the compound of the formula (VIIIa-3a)>

Among the compounds of the formula (VIIIa), the compound of the following formula (VIIIa-3a):

[0454]

[Chemical formula 70]

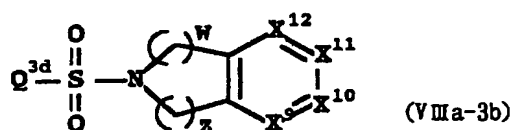


[wherein X^9 , X^{10} , X^{11} , X^{12} , Q^{3a} , w and z have the same meanings

as described above] can be obtained by removing the protecting group from the nitrogen atom of Q^{3d} of the compound which is available by the below-described preparation process and is represented by the following formula (VIIIa-3b):

[0455]

[Chemical formula 71]

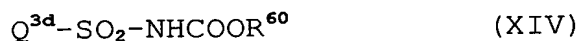


[wherein X^9 , X^{10} , X^{11} , X^{12} , Q^{3d} , w and z have the same meanings as described above].

[0456]

Described specifically, the compound represented by the following formula (XIV):

[0457]

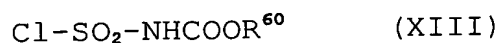


[wherein R^{60} and Q^{3d} have the same meanings as described above] can be synthesized by reacting an amino compound represented by the following formula (IIIc):

[0458]



[wherein Q^{3d} has the same meaning as described above] with a compound represented by the following formula (XIII):



[wherein R^{60} represents an easily removable group such as

tertiary butyl, benzyl, paramethoxybenzyl or paranitrobenzyl], which has been obtained from chlorosulfonyl isocyanate and an alcohol, in the presence of an appropriate base in an inert solvent.

[0459]

The compound of the formula (VIIIa-3b) can be synthesized by removing the protecting group on the nitrogen atom of the compound of the formula (XIV), thereby obtaining the compound represented by the following formula (XV):

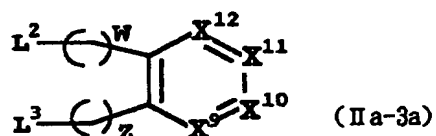
[0460]



[wherein, Q^{3d} has the same meaning as described above] and then reacting the resulting compound of the formula (XV) with a compound represented by the following formula (IIa-3a):

[0461]

[Chemical formula 72]



[wherein, X^9 , X^{10} , X^{11} , X^{12} , w and z have the same meanings as described above, L^2 and L^3 each independently represents an eliminating group frequently employed in organic chemistry such as chlorine, bromine, iodine, methylsulfonyloxy or paratoluenesulfonyloxy] in the presence of an appropriate base in an inert solvent.

[0462]

The reaction between the compounds of the formula (IIIc) and (XIII) is carried out at -70 to 100°C in an solvent, for example, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, benzene, toluene or acetone, or a mixed solvent thereof in the presence of a base such as sodium carbonate, potassium carbonate, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU), whereby the compound of the formula (XIV) can be obtained.

[0463]

The protecting group on the nitrogen atom of the compound represented by the formula (XIV) can be removed as described below. When the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or combination thereof. An arylmethyl group such as benzyloxycarbonyl, paranitrobenzyloxycarbonyl or paramethoxybenzyloxycarbonyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. The paramethoxybenzyloxycarbonyl group can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid,

phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. Thus, by the removal of the protecting group, the compound of the formula (XV) can be obtained.

[0464]

The reaction of the compound of the formula (XV) with the compound of the formula (IIa-3a) is carried out at -20 to 150°C in the presence of a base in a solvent, for example, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, a solvent such as acetone, N,N-dimethylformamide, N-methylpyrrolidin-2-one or acetamide, or a mixed solvent thereof, whereby the compound of the formula (VIII-3b) can be obtained. Examples of the base include sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0465]

The protecting group of the nitrogen atom of the compound represented by the formula (VIII-3b) can be removed by the ordinarily employed process. Described specifically, when the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric

acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can also be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIII-3a) can be obtained.

<Reaction of any one of the compounds of the formulas (IVa) to (IVd) with the compound of the formula (VIIIa)>

Examples of the carboxylic acid of each of the formulas (IVa) to (IVd) in an appropriate activated form include acid mixed acid anhydrides available by reacting the carboxylic acid of each of the formulas (IVa) to (IVd) with a chloroformate ester such as isobutyl chloroformate, thereby converting it into the corresponding acid anhydride, acid halides such as acyl chloride prepared by treating with an inorganic acid halide such as thionyl chloride, phenols such as paranitrophenol, active esters obtained by reacting with pentafluorophenyl-trifluoroacetate, active esters obtained by reacting it with N-hydroxybenztriazole or N-hydroxysuccinimide, reaction

products with N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride which is ordinarily employed in the synthesis of an amino acid, reaction products with diethyl cyanophosphonate (salting-in method) and reaction products with triphenylphosphine and 2,2'-dipyridylsulfide (Mukaiyama's method).

[0466]

The resulting carboxylic acid in an activated form is reacted with the compound of the formula (VIIIa) at -78 to 150°C, usually in the presence of an appropriate base in an inert solvent, whereby the sulfonyl derivative of the formula (I) can be obtained.

[0467]

Examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as bisilylamine such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0468]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane.

[0469]

[Preparation Process-2-(1)]

When the nitrogen atom of Q^{3a} of the compound represented by the below-described formula (VIIIa) to be acylated:



[wherein, Q^{3a} and Q^4 have the same meanings as described above] is a primary or secondary amine, preferred examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) and usable examples of the solvent include, in addition to inert solvents, alcohol solvents such as ethanol and butanol and ester solvents such as ethyl acetate.

[0470]

[Preparation Process-2-(2)]

When the nitrogen atom of Q^{3a} of the compound represented by the below-described formula (VIIIa) to be acylated:



[wherein Q^{3a} and Q^4 have the same meanings as described above] forms an amide bond, examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as bisilylamine, e.g., lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU). Examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane, dioxane and N,N-dimethylformamide.

[0471]

[Preparation Process-3]

A process for preparing, in the case the nitrogen atom of Q^{3a} of the compound represented by the following formula (VIIIa):

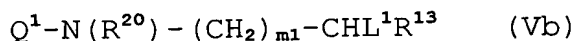


[wherein, Q^{3a} and Q^4 have the same meanings as described above] constitutes an amide, the sulfonyl derivative of the present invention by alkylating the nitrogen atom of the formula (VIIIa) with any one of the compounds represented by the following formulas (Va) to (Vd):

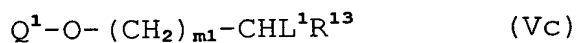
[0472]



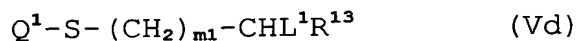
[0473]



[0474]



[0475]



[0476]

[wherein Q^1 , Q^{2b} , R^{13} , R^{20} , $m1$ and L^1 have the same meanings as described above].

[0477]

When the nitrogen atom of Q^{3a} of the compound of the formula (VIIIa) is a nitrogen atom of an amide bond, the sulfonyl derivative of the formula (I) can be synthesized by alkylating the nitrogen atom of Q^{3a} of the compound of the formula (VIIIa) with any one of the compounds of the formulas (Va) to (Vd). Described specifically, the sulfonyl derivative (I) can be obtained by reacting the compound of the formula (VIIIa) with any one of the compounds of the formulas (Va) to (Vd) at -78 to 150°C for 0.5 to 120 hours in the presence of an appropriate base in an inert solvent, thereby effecting alkylation of the nitrogen atom.

[0478]

Examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal, such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium

diisopropylamide; organometallic bases such as bisilylamine, e.g., lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU). Preferred examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane, toluene, dioxane and N,N-dimethylformamide.

[0479]

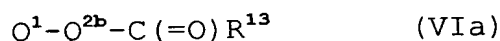
[Preparation Process-4]

A process for preparing, in the case where the nitrogen atom of Q^{3a} of the compound represented by the formula (VIIIa):

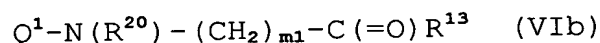


[wherein, Q^{3a} and Q^4 have the same meanings as described above] exists as a primary or secondary amine, the sulfonyl derivative (I) by forming the corresponding imine with any one of the carbonyl compounds represented by the following formulas (VIa) to (VIId):

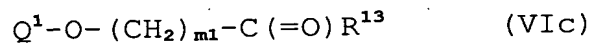
[0480]



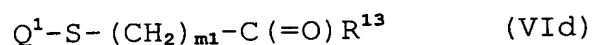
[0481]



[0482]



[0483]



[wherein Q^1 , Q^{2b} , R^{13} , R^{20} and $m1$ have the same meanings as described above], followed by reduction.

[0484]

[0485]

When the nitrogen atom of Q^{3a} of the compound of the formula (VIIIa) exists as an amine, the sulfonyl derivative of the formula (I) can be prepared by reacting the compound of the formula (VIIIa) with any one of the carbonyl compounds of the formulas (VIa) to (VIId) at -20 to 150°C for 0.5 to 120 hours, usually in an inert solvent, if necessary in the presence of an organic acid such as acetic acid, a mineral acid such as hydrochloric acid or a Lewis acid such as aluminum chloride, thereby forming the corresponding imine and then hydrogenating the resulting imine with a boron hydride reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride or a catalytic reduction catalyst such as palladium-carbon in an inert solvent at 10 to 110°C for 0.5 to 120 hours.

[0486]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane.

[0487]

[Preparation Process-5]

A process for reacting, in the case where Q^{3a} of the compound represented by the following formula (VIIIa):

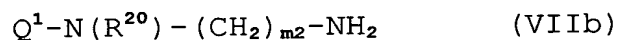


[wherein, Q^{3a} and Q^4 have the same meanings as described above]
exists as a primary or secondary amine, the compound of the
formula (VIIIa) with any one of the primary-amine-containing
compounds represented by the following formulas (VIIa) to
(VIId):

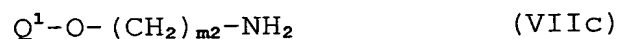
[0488]



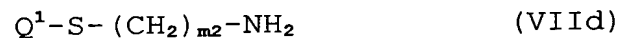
[0489]



[0490]



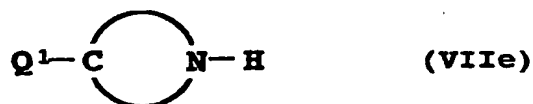
[0491]



or a secondary-amine-containing compound represented by the
following formula (VIIe):

[0492]

[Chemical formula 73]



[in the above-described formulas, Q^1 , Q^{2b} , R^{20} , $m2$ and the group:

[0493]

[Chemical formula 74]



have the same meanings as described above] by using a reagent such as phosgene, triphosgene or carbonyldiimidazole, thereby forming the corresponding urea derivative.

[0494]

When Q^{3a} of the compound of the formula (VIIIa) exists as an amine, the compound of the formula (VIIIa) is reacted with any one of the primary-amine-containing compounds represented by the formulas (VIIa) to (VIId) or the secondary-amine-containing compound represented by the formula (VIIe) and a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole to introduce it into the sulfonyl derivative of the present invention represented by the formula (I), which is to be an urea derivative.

[0495]

The synthesis can be carried out by successively reacting a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole with any one of the primary-amine-containing compounds of the formulas (VIIa) to (VIId) or the secondary-amine-containing compound of the formula (VIIe) and the compound of the formula (VIIIa), if necessary in the presence of a base, in an inert solvent. Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene,

N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane. Among them, dichloromethane, tetrahydrofuran and toluene are preferred.

[0496]

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction may be conducted at a temperature range of from -70°C to 110°C.

[0497]

[Preparation Process-6]

A process for preparing a urea-containing sulfonyl derivative of the formula (I) by reacting, in the case where the nitrogen atom of Q^{3a} of the compound represented by the formula (VIIIa):

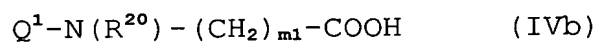


[wherein, Q^{3a} and Q^A have the same meanings as described above] exists as a primary or secondary amine, the amine of the formula (VIIIa) with a known isocyanate derivative ($Q^1-Q^{2b}-N=C=O$) [wherein, Q^1 and Q^{2b} have the same meanings as described above] or an isocyanate prepared from any one of the carboxylic acids represented by the following formulas (IVa) to (IVd):

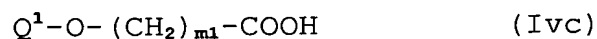
[0498]



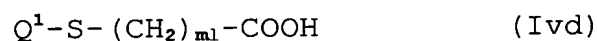
[0499]



[0500]



[0501]



[wherein Q^1 , Q^{2b} , R^{20} and $m1$ have the same meanings as described above].

[0502]

When Q^{3a} of the compound represented by the formula (VIIIa) is an amine, the sulfonyl derivative of the formula (I) can be prepared by reacting the compound of the formula (VIIIa) with a known isocyanate derivative at -20 to 100°C for 0.5 to 120 hours in an inert solvent.

[0503]

The isocyanate derivative can be synthesized from any one of the carboxylic acids of the formulas (IVa) to (IVd). Described specifically, it can be obtained by introducing any one of the carboxylic acids of the formulas (IVa) to (IVd) into the corresponding acid halide with thionyl chloride, oxalyl chloride or the like, reacting the resulting acid halide with sodium azide at a temperature range of from 0 to 60°C in an inert solvent and then, heating the reaction mixture; by reacting the carboxylic acid of the formula (IVa) with a chloroformate such

as isobutyl chloroformate, reacting the resulting acid anhydride with sodium azide and then heating the reaction mixture; or introducing any one of the carboxylic acids represented by the formulas (IVa) to (IVd) into the corresponding hydrazide through an ester in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C, reacting the resulting hydrazide with nitrous acid or alkyl ester thereof to introduce it into the corresponding acyl azide and then heating at 20 to 150°C in a solvent such as chloroform, dichloroethane, toluene, xylene or N,N-dimethylformamide.

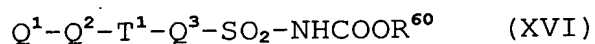
[0504]

The sulfonyl derivative of the formula (I) can also be prepared by reacting any one of the carboxylic acids of the formulas (IVa) to (IVd) with diphenylphosphorylazide at 10 to 100°C in the presence of a base such as triethylamine in an inert solvent and then reacting the reaction mixture with the amine of the formula (VIIIa).

[Preparation Process-7]

The compound represented by the following formula (XVI):

[0505]



[wherein, Q^1 , Q^2 , Q^3 , R^{60} and T^1 have the same meanings as described above] can be synthesized by reacting, in the case where the nitrogen atom of Q^{3a} of the compound represented by the following formula (Ia) to be sulfonylated:

[0506]



[wherein, Q^1 , Q^2 , Q^{3a} and T^1 have the same meanings as described above] exists as a primary or secondary amine, the compound of the formula (Ia) with a compound which is available from chlorosulfonyl isocyanate and an alcohol and is represented by the following formula (XIII):



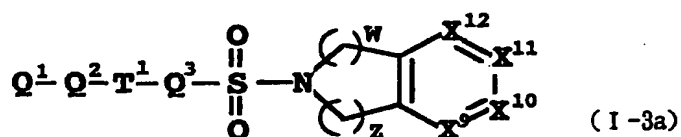
[wherein, R^{60} has the same meaning as described above] in the presence of an appropriate base in an inert solvent.

[0507]

The compound represented by the following formula (I-3a):

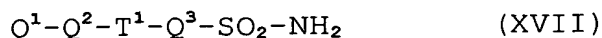
[0508]

[Chemical formula 76]



[wherein, Q^1 , Q^2 , Q^3 , T^1 , X^9 , X^{10} , X^{11} , X^{12} , w and z have the same meanings as described above], one of the compounds of the formula (I), can be synthesized by removing the protecting group on the nitrogen atom of the resulting compound (XVI), thereby obtaining a compound represented by the following formula (XVII):

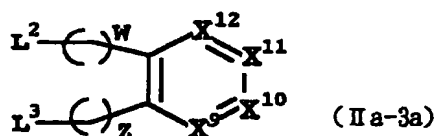
[0509]



[wherein, Q^1 , Q^2 , Q^3 and T^1 have the same meanings as described above]; and then reacting the resulting compound of the formula (XVII) with a compound represented by the following formula (IIa-3a):

[0510]

[Chemical formula 75]



[wherein, X^9 , X^{10} , X^{11} , X^{12} , L^2 , L^3 , w and z have the same meanings as described above] in an appropriate base in an inert solvent.

The reaction between the compound of the formula (Ia) and the compound of the formula (XIII) to synthesize the compound of the formula (XVI) is effected at -70 to 100°C in an solvent, for example, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, or a solvent such as benzene, toluene or acetone or a mixed solvent thereof and in this reaction, usable examples of the base include sodium carbonate, potassium carbonate and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0511]

The protecting group on the nitrogen atom of the compound of the formula (XVI) can be removed as described below. When

the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or combination thereof. An arylmethyl group such as benzyloxycarbonyl, paranitrobenzyloxycarbonyl or paramethoxybenzyloxycarbonyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. The paramethoxybenzyloxycarbonyl group can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. Thus, by the removal of the protecting group, the compound of the formula (XVII) can be obtained.

[0512]

The reaction of the compound of the formula (XVII) with the compound of the formula (IIa-3a) is carried out at -20 to 150°C in the presence of a base in a solvent, for example, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, a solvent such as acetone, N,N-dimethylformamide, N-methylpyrrolidin-2-one or acetamide, or a mixed solvent thereof, whereby the compound of the formula (I-3a), one of the compounds of the formula (I), can be obtained.

[0513]

Examples of the base include sodium carbonate, potassium carbonate, and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

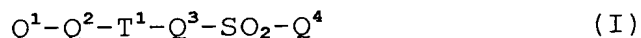
[0514]

From the compound of the formula (I-3a), it is possible to eliminate the protecting group in an ordinarily employed process if necessary.

[0515]

[Preparation Process-8]

A process for synthesizing a sulfonyl derivative represented by the following formula (I):



[wherein, Q^1 , Q^2 , Q^3 , Q^4 , T^1 have the same meanings as described above] by coupling reaction using a transition metal catalyst.

[0516]

When in the structure of Q^1 of the sulfonyl derivative of the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, it can be subjected to coupling reaction with a boric-acid-substituted aryl compound in the presence of a transition metal catalyst.

[0517]

When in the structure of Q^1 of the sulfonyl derivative of the formula (I), an alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group in the presence of a transition metal catalyst.

[0518]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), a boric-acid-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl compound or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl compound.

[0519]

When in the structure of Q^1 of the sulfonyl derivative of the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group is contained, the sulfonyl derivative of the formula (I) can be obtained by coupling with an alkenyl compound in the presence of a transition metal catalyst. The sulfonyl derivative of the formula (I) thus obtained may be deprotected as needed.

[0520]

When in the structure of Q^1 of the sulfonyl derivative of the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is

contained, it can be subjected to coupling reaction with a boric-acid-substituted aryl derivative by using a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (O), in a two-phase solvent such as benzene-water or toluene-water, an amide solvent such as N,N-dimethylformamide or an ether solvent such as tetrahydrofuran or dimethoxyethane, in the presence of a base such as sodium carbonate, sodium hydroxide, barium hydroxide, potassium phosphate or cesium carbonate or a neutral salt such as cesium fluoride at a temperature range of 20 to 150°C for 0.5 to 120 hours.

[0521]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), a boric-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl compound or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl derivative.

[0522]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), an alkenyl group or boric-acid-substituted alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group by using a transition metal catalyst such as palladium acetate, in the presence of an appropriate base, in an amide solvent such as N,N-dimethylformamide at a temperature range of from 20 to 150°C

for 0.5 to 120 hours.

[0523]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), a boric-acid-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl derivative or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl derivative.

[0524]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group, it can be subjected to coupling reaction with an alkenyl compound by using a transition metal catalyst. By the above-described process, the sulfonyl derivative of the formula (I) can be obtained. By deprotection of the resulting sulfonyl derivative of the formula (I) as needed, the sulfonyl derivative of the formula (I) having a changed substituent can be obtained.

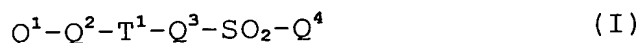
[0525]

[Preparation Process-9]

A process for preparing an amidoxime type sulfonamide product:

When T^1-Q^3 of the sulfonyl derivative represented by the following formula (I):

[0526]

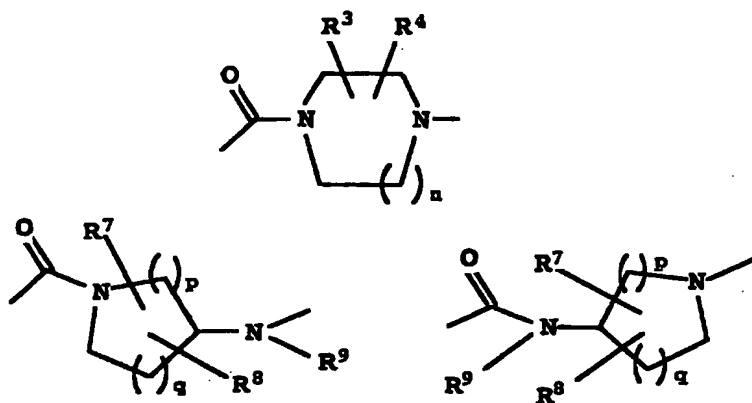


[wherein Q^1 , Q^2 , Q^3 , Q^4 and T^1 have the same meanings as described

above] represents any one of the following formulas:

[0527]

[Chemical formula 77]



[wherein R^3 , R^4 , R^7 , R^8 and R^9 have the same meanings as described above, n stands for an integer of 1 or 2, p stands for an integer of 1 to 3 and q stands for an integer of 0 to 3 with the proviso that the sum of p and q stands for an integer of 3 or 4] and none of amine-, alkylamine-, amido-, hydroxyl- and carboxylic-acid-containing substituents exist on R^3 , R^4 , R^7 , R^8 , R^9 or a substituent replaceable therewith in Q^1 , Q^2 and Q^3 of the formula (I), the sulfonyl derivative of this type represented by the formula (I) can be obtained by reacting the sulfonyl derivative of the formula (I) with a halogenating agent such as phosphorous oxychloride or phosphorus pentachloride or an alkylating agent such as Meerwein reagent at -30 to 140°C , if necessary in an inert solvent, for example, a halogen solvent such as chloroform at 0 to 80°C , to convert the derivative into the corresponding imino chloride or imino ether and then, reacting the resulting imino chloride or imino ether with

hydroxylamine, alkoxyamine which may have a substituent or salt thereof at 0 to 80°C, preferably at 20 to 60°C, if necessary in the presence of a base catalyst.

[0528]

Examples of the inert solvent include alkyl halide solvents such as dichloromethane, chloroform and carbon tetrachloride, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane and aromatic solvents such as benzene and toluene. Among them, the alkyl halide solvents are particularly preferred. Examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by an alkyl lithium such as n-butyl lithium and a dialkylamino lithium such as lithium diisopropylamide; organometallic bases such as bisilylamine, e.g., lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0529]

[Preparation Process-10]

N-oxide formation

When in the sulfonyl derivative of the formula (I), there

exists a nitrogen-containing heterocyclic aromatic ring or aliphatic tertiary amine on Q^1 , Q^2 , Q^3 , Q^A or T^1 or a substituent replaceable therewith, the sulfonyl derivative of the formula (I) is reacted with a peroxide such as hydrogen peroxide, metachloroperbenzoic acid or tertiary butyl hydroperoxide at -40 to 60°C for 0.5 to 120 hours preferably -20 to 20°C in a solvent such as water or acetic acid, a benzene solvent such as benzene, toluene or xylene, an ether solvent such as tetrahydrofuran or dimethoxyethane or an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, whereby the sulfonyl derivative of the formula (I) can be obtained as an N-oxide derivative.

[0530]

[Preparation Process-11]

Quaternization of a nitrogen atom

When in the sulfonyl derivative of the formula (I), there exists a nitrogen-containing heterocyclic aromatic group or aliphatic tertiary amine on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, the sulfonyl derivative of the formula (I) is reacted with an alkyl halide such as methyl iodide or ethyl iodide in an ether solvent such as 1,2-dimethoxyethane or dioxane, an aromatic solvent such as benzene or toluene, an amide solvent such as N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidin-2-one or a sulfoxide solvent such as dimethyl sulfoxide or sulfolane at -10 to 150°C , preferably 0 to 80°C , whereby the sulfonyl derivative of the

formula (I) can be obtained as a quaternary amino product.

[0531]

[Preparation Process-12]

Sulfoxide or sulfone formation

When in the sulfonyl derivative of the formula (I), a sulfur-containing hetero ring or aliphatic thioether exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, the sulfonyl derivative of the formula (I) is reacted with a peroxide such as hydrogen peroxide, metachloroperbenzoic acid or tertiary butyl hydroperoxide at -40 to 60°C for 0.5 to 120 hours, preferably -20 to 20°C in a solvent such as water or acetic acid, a benzene solvent such as benzene, toluene or xylene, an ether solvent such as tetrahydrofuran or dimethoxyethane or an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, whereby the sulfonyl derivative (I) can be obtained in the form of sulfoxide or sulfone.

[0532]

[Preparation Process-13]

Amidino formation-1

When in the sulfonyl derivative of the formula (I), a nitrile group exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, it can be converted into an amidino group by an ordinarily employed process. The amidino-containing sulfonyl derivative of the formula (I) can be obtained, for example, by allowing an equal amount to large excess of a C_{1-4} alcohol such as methanol, ethanol or propanol to act on the

sulfonyl derivative of the formula (I) at -10 to 60°C for 3 to 120 hours in an aliphatic ether solvent such as diethyl ether, an alkyl halide solvent such as chloroform or dichloromethane or an aprotic solvent such as benzene or a mixed solvent thereof in the presence of a hydrogen halide such as hydrogen chloride or hydrogen bromide, thereby converting it to the corresponding imino ether; then reacting the resulting imino ether product with ammonium, a monoalkylamine which may have a substituent or a dialkylamine which may have a substituent, or a carbonate or acetate thereof at -10 to 140°C for 0.5 to 200 hours in a C₁₋₄ alcohol such as ethanol or propanol, an aliphatic ether solvent such as diethyl ether, an alkyl halide solvent such as chloroform, an aprotic solvent such as benzene, a solvent such as N,N-dimethylformamide or dimethylsulfoxide or a mixed solvent thereof, preferably at -8 to 30°C for 10 to 96 hours in ethanol.

[0533]

[Preparation Process-14]

Amidino formation-2

When in the sulfonyl derivative of the formula (I), a primary or secondary amino group exists on Q¹, Q², Q³, Q^A or T¹ or a substituent replaceable therewith, it can be converted into a substituted amidino group by an ordinarily employed process.

[0534]

Described specifically, the amidino-containing sulfonyl derivative of the formula (I) can be obtained, for example, by

reacting the sulfonyl derivative of the formula (I) with an imino ether, imino chloride or salt thereof, which has been synthesized from an amide compound or nitrile compound, in an aliphatic ether solvent such as diethyl ether, an alkyl halide solvent such as chloroform or dichloromethane or an aprotic solvent such as benzene, or a mixed solvent thereof, if necessary in the presence of a base catalyst, at -10 to 140°C for 0.5 to 200 hours, preferably 0 to 80°C for 10 to 96 hours. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0535]

[Preparation Process-15]

N-nitrile formation

When in the sulfonyl derivative of the formula (I), a primary or secondary amine group exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, it can be cyanated by an ordinarily employed process.

[0536]

For example, the sulfonyl derivative of the formula (I) is reacted with cyan bromide in an alcohol solvent such as methanol, ethanol or propanol in the presence of a salt such

as sodium acetate or a base at -10 to 110°C, preferably 0 to 60°C, whereby the sulfonyl derivative (I) having on the nitrogen atom thereof a nitrile group can be obtained. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0537]

[Preparation Process-16]

Amidoxime or carboxamido-O-alkyloxime introduction

When in the sulfonyl derivative of the formula (I), a nitrile group exists on Q¹, Q², Q³, Q⁴ or T¹ or a substituent replaceable therewith, it can be converted into an amidoxime or carboxamido-O-alkyloxime group by an ordinarily employed process.

[0538]

For example, the sulfonyl derivative of the formula (I) is reacted with hydroxylamine or an alkoxyamine which may have a substituent, or salt thereof in an alcohol solvent such as methanol, ethanol or propanol, an ether solvent such as diethyl ether or tetrahydrofuran, a halogenated hydrocarbon such as chloroform or dichloromethane, an aprotic solvent such as toluene, an amide solvent such as N,N-dimethylformamide or a

solvent such as dimethylsulfoxide, or a mixed solvent thereof at -10 to 110°C, preferably 0 to 60°C, if necessary in the presence of a base catalyst, whereby the sulfonyl derivative of the formula (I) having an amidoxime or carboxamido-O-alkyloxime group can be obtained. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0539]

[Preparation Process-17]

Guanidino introduction

When in the sulfonyl derivative of the formula (I), a primary or secondary amino group exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, it can be converted into a substituted or unsubstituted guanidino group by an ordinarily employed process.

[0540]

For example, the sulfonyl derivative of the formula (I) having a primary or secondary amino group is reacted with N,N'-di(tert-butoxy)carbonylthiourea and N,N'-dicyclohexylcarbodiimide as a condensing agent in an aliphatic ether solvent such as diethyl ether, a halogenated hydrocarbon such as chloroform or dichloromethane or an aprotic solvent such

as benzene, or a mixed solvent thereof at -10 to 140°C for 0.5 to 200 hours, preferably 0 to 80°C for 10 to 96 hours, if necessary in the presence of a base catalyst, and then, as usual, the tertiary butoxycarbonyl group is removed, whereby the sulfonyl derivative of the formula (I) as a guanidino compound can be synthesized. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0541]

[Preparation Process-18]

Deprotection from the protected nitrogen atom

When in the sulfonyl derivative of the formula (I), an acylamino or alkoxycarbonylamino group exists on Q¹, Q², Q³, Q⁴ or T¹ or a substituent replaceable therewith, an amino-containing derivative can be obtained by subjecting the derivative to hydrolysis at 0 to 80°C in a solvent such as water, a lower alcohol or tetrahydrofuran, or a mixed solvent thereof in the presence of a base such as an alkali metal hydroxide, e.g., lithium hydroxide, sodium hydroxide or potassium hydroxide. The nitrogen atom to which an acyl type protecting group such as tertiary butoxycarbonyl or paramethoxybenzyloxycarbonyl has been bonded can be converted

into a nitrogen-hydrogen bond by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof in a solvent such as water, an alcohol solvent such as methanol, an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, an ether solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane or an aromatic solvent such as benzene or toluene and removing the acyl type protecting group from the nitrogen atom at 0 to 80°C.

[0542]

The nitrogen atom to which an arylmethoxycarbonyl group such as benzyloxycarbonyl, paramethoxybenzyloxycarbonyl or para(ortho)-nitrobenzyloxycarbonyl has been bonded can be converted into a nitrogen-hydrogen bond by removing the arylmethoxycarbonyl group from the protected nitrogen atom through hydrogenolysis in the presence of a palladium-carbon catalyst in a solvent such as water, an alcohol solvent such as methanol or ethanol, an ester solvent such as ethyl acetate, an ether solvent such as diethyl ether or tetrahydrofuran, or a solvent such as acetic acid or N,N-dimethylformamide, or a mixed solvent thereof. The nitrogen atom to which a silyl type protecting group such as trimethylsilyl or tertiary butyl dimethylsilyl has been bonded can be converted into a nitrogen-hydrogen bond by reacting with hydrochloric acid or a hydrofluoride such as tetrabutylammonium fluoride at 0 to 80°C

in an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, an ether solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane or an aromatic solvent such as benzene or toluene, thereby removing the silyl group from the protected nitrogen atom. The nitrogen atom to which a benzyl group has been bonded can be converted into a nitrogen-hydrogen bond by removing the benzyl group through the catalytic reduction at 0 to 80°C with a palladium-carbon catalyst or the like in a solvent such as ethanol, tetrahydrofuran or acetic acid or through the Birch's reduction with a metal sodium in a liquid ammonia. The nitrogen atom to which a triphenylmethyl group has been bonded can be converted into a nitrogen-hydrogen bond by removing the triphenylmethyl group through the catalytic reduction with a palladium-carbon catalyst or the like at 0 to 80°C in a solvent such as ethanol, tetrahydrofuran or acetic acid or through the Birch's reduction with a metal sodium in a liquid ammonia. The removal of the triphenylmethyl group and conversion into a nitrogen-hydrogen bond can also be carried out by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or a combination thereof at 0 to 80°C.

[0543]

[Preparation Process-19]

Ester hydrolysis

When in the sulfonyl derivative of the formula (I), an alkoxy carbonyl group exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, in the case of a methyl or ethyl ester, the alkoxy carbonyl group can be converted into the corresponding carboxylic acid by the hydrolysis with an appropriate base, for example, an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide. In the case of a tertiary butyl ester, the tertiary butyl group can be removed by treating with trifluoroacetic acid or hydrochloric acid, while in the case of an arylmethyl type ester such as benzyl, the carboxylic acid can be obtained by removing the arylmethyl group by hydrogenolysis in the presence of a palladium-carbon catalyst. Conversion from an ester group to a carboxylic acid residue can be effected using potassium trimethylsilanolate.

[0544]

[Preparation Process-20]

When in the sulfonyl derivative of the formula (I), an acyloxy, arylmethoxy, silylether, methoxymethyl or tetrahydropyranyl group exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, the acyl group such as alkanoyl or aroyl can be removed by the hydrolysis with an appropriate base, for example, an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide; or alternatively can be removed by reacting with an organic base such as ammonia or

methylamine. The arylmethyl type protecting group can be removed by the hydrogenolysis with a palladium-carbon catalyst. The silylether group such as tertiary butyl dimethylsilyl can be removed by a hydrofluoride salt such as tetrabutylammonium fluoride. The methoxymethyl or tetrahydropyranyl group can be removed using acetic acid or hydrochloric acid.

[0545]

[Preparation Process-21]

When in the sulfonyl derivative of the formula (I), an amino group exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, it can be acylated by an ordinarily employed process which uses an acyl halide or activated carboxylic acid. Alternatively, it can be alkylated by reductive alkylation or the like process. The sulfonyl derivative of the formula (I) which is an urea derivative can be prepared by sulfonylation through sulfonic acid chloride or by reacting with isocyanate or carboxylic-acid-derived isocyanate.

[0546]

[Preparation Process-22]

When in the sulfonyl derivative of the formula (I), a carboxyl group exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, it can be converted into a carbamoyl, alkylcarbamoyl or dialkylcarbamoyl group by an ordinarily employed active ester method or mixed acid anhydride method and then converted into a hydroxyl or aldehyde group by reduction. The resulting hydroxyl or aldehyde group can be subjected to conversion of

a functional group, such as ether bond formation, conversion into an amino group or conversion into an alkylamino group by the process ordinarily employed in organic chemistry. The carboxyl group, after conversion into its ester or mixed acid anhydride directly or by the usual process, is reduced, whereby the corresponding alcohol can be obtained.

[0547]

[Preparation-23]

Formation of phenol

When in the sulfonyl derivative of the formula (I), an aryl-substituted methoxy group exists on Q^1 , Q^2 , Q^3 , Q^4 or T^1 or a substituent replaceable therewith, it can be converted into a hydroxyl group by removing the methyl group using thylsilyl iodide at -78 to 110°C in an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride or a benzene solvent such as toluene, or at -78 to 110°C in a Lewis acid such as aluminum chloride, phosphorus tribromide or boron trifluoride, an alkyl halide solvent or an ether solvent.

[0548]

[Preparation process-24]

Conversion of a halogen atom into an alkynyl group

When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula

(VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) has an aromatic ring substituted with chlorine, bromine or iodine, such a halogen atom can be converted into an acetylene group by reacting with a silylacetylene compound in the presence of a transition metal catalyst.

[0549]

The conversion of chlorine, bromine or iodine into a silylacetylene group can be carried out by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) having an aromatic ring substituted with chlorine, bromine or iodine, with a silylacetylene such as trimethylsilylacetylene by using palladium acetate and triphenylphosphine at a temperature range of from -20 to 150°C for 0.5 to 120 hours, if necessary in the presence of a base such as triethylamine or pyridine, in a benzene solvent such as toluene, an ether solvent such as tetrahydrofuran or an amide solvent such as N,N-dimethylformamide, or a mixed solvent thereof.

[0550]

The silyl group can be removed from the resulting silylacetylene compound by treating the compound with a base such as potassium carbonate, potassium bicarbonate or sodium hydroxide in a solvent, for example, an alcohol solvent such as methanol, an ether solvent such as tetrahydrofuran, water, or a mixed solvent thereof.

[0551]

[Preparation Example-25]

Conversion of a halogen atom into a nitrile group

When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) has an aromatic ring substituted with chlorine, bromine or iodine, such a halogen atom can be converted into a nitrile group by reacting with zinc cyanide in the presence of a transition metal catalyst. The conversion of chlorine, bromine or iodine into a nitrile group can be carried out by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of

the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) having an aromatic ring substituted with chlorine, bromine or iodine, with zinc cyanide by using a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (0) at a temperature range of from -20 to 150°C for 0.5 to 120 hours, if necessary in the presence of an appropriate base such as triethylamine or pyridine, in a benzene solvent such as toluene, an ether solvent such as tetrahydrofuran or an amide solvent such as N,N-dimethylformamide, or a mixed solvent thereof.

[0552]

[Preparation process-26]

Conversion of a halogen atom into a trifluoromethyl group

When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) contains chlorine, bromine or iodine as a substituent, such a halogen atom can be converted into a trifluoromethyl group by reacting the compound with a trifluoromethylating reagent in the presence of a metal catalyst. Described specifically, the conversion of chlorine,

bromine or iodine into a trifluoromethyl group can be effected by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) containing chlorine, bromine or iodine as a substituent, with a trifluoromethylating reagent such as methyl 2,2-difluoro-2-(fluorosulfonyl)acetate in the presence of a metal catalyst such as copper iodide at a temperature range of from 0 to 150°C for 0.5 to 120 hours in a benzene solvent such as toluene, an ether solvent such as tetrahydrofuran or an amide solvent such as N,N-dimethylformamide, or a mixed solvent thereof.

[0553]

[Preparation process-27]

Conversion of a nitrile group into a tetrazole group

When the compound of the formula (I) has a nitrile group as a substituent, it can be converted into the compound of the formula (I) having a tetrazole group by reacting the former with sodium azide or trimethylsilyl azide at 0 to 170°C in the presence of trimethylaluminum or di-n-butyltin oxide in a benzene solvent such as benzene or toluene.

[0554]

[Preparation process-28]

Conversion of an amidino group into an alkoxycarbonylamidino group

When the compound of the formula (I) contains an amidino group, it can be converted into the compound of the formula (I) containing an alkoxycarbonylamidino group by reacting the former with a reagent, for example, an acid chloride such as alkyl chlorocarbonate or alkyl p-nitrobenzylcarbonate at -78 to 100°C in the presence of a base in an alkyl halide solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or an ether solvent such as tetrahydrofuran.

[0555]

Examples of the base include sodium carbonate, potassium carbonate, pyridine, 2,6-lutidine, 4-dimethylaminopyridine, diazabicyclo[5.4.0]undec-7-en (DBU).

[0556]

The sulfonyl derivative of the formula (I) according to the present invention, salt thereof or solvate thereof has peculiar and excellent FXa inhibitory activity and is therefore useful as a coagulation suppressor or a preventive and/or remedy for thrombosis or embolism.

[0557]

The sulfonyl derivative of the present invention exhibits effects even by the oral administration so that it can be

administered either orally or parenterally. The dose of the sulfonyl derivative can be changed as needed depending on the symptom, age, weight and/or the like of a patient. In general, it is necessary to administer the derivative in an amount of 1 to 1000 mg/day, preferably 5 to 300 mg/day per adult. Although no particular limitation is imposed on the dosage form, examples include tablets, capsules, powders, granules, suspensions, syrups and dry syrups. The derivative together with ordinarily employed additives such as excipient, lubricant or binder can be formulated into the above-described dosage forms in accordance with the known formulation technique.

[0558]

No particular limitation is imposed on the dosage form in the case of parenteral administration but examples include ointments, plasters, injections and suppositories. As an injection, the derivative may be administered subcutaneously or intravenously or by intravenous drip in an amount of 0.1 to 100 mg/day, preferably 0.5 to 30 mg/day per adult.

[0559]

The sulfonyl derivatives of the present invention exhibit anticoagulant action based on excellent FAX inhibitory action. Accordingly, the sulfonyl derivative of the present invention can treat or prevent various diseases caused by thrombosis or embolism, for example, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis and

disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization, formation of thrombus upon extracorporeal circulation and blood coagulation upon blood collection without acting on platelets.

[0560]

The present invention will hereinafter be described more specifically by Referential Examples, Examples and Tests. It should however be borne in mind that the present invention is not limited to or by them.

[0561]

[Examples]

The sulfonyl derivative of the present invention and preparation process therefor will next be described specifically. Incidentally, the starting compounds for the sulfonyl derivative of the present invention contain novel compounds and such compounds and preparation process therefor will be described in Referential Examples.

[0562]

Upon preparation of the compound, Merck Silica Gel 60 or Yamazen Silica Gel for moderate pressure liquid chromatography were employed for silica gel column chromatography.

[0563]

In the nuclear magnetic resonance spectrum (NMR), tetramethylsilane was used as an internal standard.

[0564]

[Referential Example 1]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazine
hydrochloride and trifluoroacetate

In dichloromethane (20 ml), tert-butyl 1-piperazine carboxylate (856 mg) was dissolved. To the resulting solution, triethylamine (0.77 ml) and 6-chloro-2-naphthylsulfonylchloride (WO96/10022) (1.20 g) were added, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed with 1N hydrochloric acid. The organic layer extracted was dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was dissolved in saturated ethanol hydrochloride (10 ml), followed by concentration under reduced pressure and washing with ethyl acetate, whereby the hydrochloride (1.62 g, quant.) of the title compound was obtained as a colorless solid.

[0565]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.1-3.4 (8H, m), 7.75 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.86 (1H, dd, $J=8.8, 1.5\text{Hz}$), 8.22 (1H, d, $J=8.8\text{Hz}$), 8.26-8.32 (2H, m), 8.56 (1H, s), 8.63 (2H, br s).

MS (FAB) m/z : 311 $[(M+H)^+, \text{Cl}^{35}]$, 313 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}\cdot\text{HCl}\cdot 0.1\text{H}_2\text{O}$

Calculated: C, 48.17; H, 4.68, Cl, 20.31; N, 8.03; S, 9.19.

Found: C, 47.91; H, 4.68; Cl, 20.41; N, 7.80; S, 9.21.

[0566]

Instead of the saturated ethanol hydrochloride, treatment was carried out using trifluoroacetic acid, whereby the trifluoroacetate was obtained.

Elementary analysis for $C_{14}H_{15}ClN_2O_2S \cdot CF_3CO_2H$

Calculated: C, 45.24; H, 3.80, Cl, 8.35; F, 13.42; N, 6.59; S, 7.55.

Found: C, 44.84; H, 3.80; Cl, 8.27; F, 13.72; N, 6.29; S, 7.50.

[0567]

[Referential Example 2]

1-[(E)-4-Chlorostyrylsulfonyl]piperazine hydrochloride

In the same manner as in Referential Example 1, a reaction was conducted using tert-butyl-1-piperazinecarboxylate and (E)-4-chlorostyrylsulfonyl chloride (W096/10022) as raw materials, whereby the title compound was obtained.

[0568]

1H -NMR (DMSO- d_6) δ : 3.20 (4H, br s), 3.33-3.38 (4H, m), 7.47 (2H, s), 7.53 (1H, d, $J=8.8$ Hz), 7.82 (1H, d, $J=8.8$ Hz).

Elementary analysis for $C_{12}H_{15}ClN_2O_2S \cdot HCl$

Calculated: C, 44.59; H, 4.99, Cl, 21.94; N, 8.67; S, 9.92.

Found: C, 44.42; H, 4.78, Cl, 21.83; N, 8.68; S, 9.87.

[0569]

[Referential Example 3]

4-tert-Butoxycarbonyl-1-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine

In dichloromethane (18 ml), 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperazine (517 mg) and 6-chloro-2-naphthylsulfonyl chloride (WO96/10022) (588 mg) were dissolved under ice cooling. To the resulting solution, diisopropylethylamine (0.59 ml) was added, followed by stirring at room temperature for 63 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby the title compound (688 mg, 71%) was obtained.

[0570]

¹H-NMR (CDCl₃)δ: 1.05 (3H, t, J=7.1Hz), 1.38 (9H, s), 2.80-4.70 (9H, m), 7.55 (1H, dd, J=8.6, 2.2Hz), 7.77 (1H, dd, J=8.6, 1.7Hz), 7.85-7.90 (3H, m), 8.33 (1H, s).

MS (FAB) m/z: 483[(M+H)⁺, Cl³⁵], 485[(M+H)⁺, Cl³⁷].

[0571]

[Referential Example 4]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

Homopiperazine (5 g) was dissolved in tetrahydrofuran (100 ml) at room temperature. To the resulting solution, 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (12.3 g) was added in portions, followed by stirring for 3 hours. After completion of the reaction, the solvent was distilled off. The residue was purified by chromatography on a silica gel column

(10 to 20% methanol - dichloromethane), followed by the addition of ethanolic 1N hydrochloric acid. The solvent was then distilled off. The residue was solidified by the addition of ethanol, whereby powders (7.46 g) were obtained. The resulting powders were reacted as in Referential Example 1, whereby the title compound was obtained.

[0572]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.00 (2H, br s), 3.10-3.30 (4H, m), 3.30-3.50 (2H, m), 3.55-3.65 (2H, m), 7.72 (1H, d, $J=8.8\text{Hz}$), 7.89 (1H, d, $J=8.3\text{Hz}$), 8.17 (1H, d, $J=8.8\text{Hz}$), 8.22-8.28 (2H, m), 8.56 (1H, s), 9.29 (2H, br s).

MS (FAB) m/z : 325 ($\text{M}+\text{H}$) $^+$.

Elementary analysis for $\text{C}_{15}\text{H}_{17}\text{ClN}_2\text{O}_2\text{S}\cdot\text{HCl}$

Calculated: C, 49.89; H, 5.02; N, 7.75; Cl, 19.63.

Found: C, 49.94; H, 5.05; N, 7.47; Cl, 19.65.

[0573]

[Referential Example 5]

(2RS)-2-(N-tert-Butoxycarbonylaminomethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene

In dimethylformamide (25 ml), (2RS)-6-methoxycarbonyl-2-toluenesulfonyloxymethyl-1,2,3,4-tetrahydronaphthalene (2.56 g) was dissolved. Sodium azide (0.92 g) was added to the resulting solution, followed by stirring at an external temperature of about 50°C for 14 hours. The reaction mixture was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate, washed with water and then dried

over sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (35 ml). Triphenylphosphine (1.82 g) was added to the resulting solution, followed by stirring at an external temperature of about 50°C for 21 hours. After about 28% aqueous ammonia (15 ml) was added and the resulting mixture was stirred for 3 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was extracted with diethyl ether. Dilute hydrochloric acid was added to the extract to make it acidic and water layer was separated. To the resulting water layer, a dilute aqueous solution of sodium hydroxide was added to make it alkaline, followed by extraction with dichloromethane. The extract was dried over sodium sulfate and distilled under reduced pressure to remove the solvent. The resulting residue was dissolved in dichloromethane (15 ml). To the resulting solution, a solution of di-tert-butyl dicarbonate (1.80 g) in dichloromethane (5 ml) was added under ice cooling, followed by stirring at room temperature for 2 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (30 g of silica gel, dichloromethane ~ dichloromethane : methanol = 50:1) and recrystallized from a mixed solvent of n-hexane and ethyl acetate, whereby colorless crystals (1.56 g, 71%) were obtained.

[0574]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40-1.60 (1H, m), 1.46 (9H, s), 1.90-2.10 (2H, m),

2.50 (1H, dd, $J=17.1, 10.7\text{Hz}$), 2.70-3.00 (3H, m), 3.10-3.30 (2H, m), 3.89 (3H, s), 4.68 (1H, br), 7.12 (1H, d, $J=7.8\text{Hz}$), 7.70-7.80 (2H, m).

Elementary analysis for $\text{C}_{18}\text{H}_{25}\text{NO}_4$

Calculated: C, 67.69; H, 7.89; N, 4.39.

Found: C, 67.78; H, 7.61; N, 4.12.

[0575]

[Referential Example 6]

1-[[[(6RS)-6-(N-tert-Butoxycarbonylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (5 ml), (2RS)-2-(N-tert-butoxycarbonylaminomethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene (0.14 g) was dissolved. To the resulting solution, 1N sodium hydroxide (0.50 ml) was added, followed by stirring at room temperature for 3 days and at an external temperature of about 50°C for 20 hours. 1N Sodium hydroxide (0.40 ml) was added further, followed by stirring at an external temperature of about 50°C for 2 days. After the reaction mixture was concentrated under reduced pressure, dichloromethane and dilute hydrochloric acid were added and the organic layer was collected. The organic layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was dissolved in N,N-dimethylformamide (5 ml). To the resulting solution 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

(0.19 g), N-methylmorpholine (0.05 ml), 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (86.0 mg) and 1-hydroxybenzotriazole (71.0 mg) were added, followed by stirring at room temperature for 18 hours. After the reaction mixture was concentrated under reduced pressure, the concentrate was diluted with ethyl acetate and washed with water. The mixture was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), whereby the title compound was obtained as a colorless oil (0.23 g, 86%).

[0576]

¹H-NMR (CDCl₃) δ: 1.30-1.60 (1H, m), 1.45 (9H, s), 1.80-2.00 (2H, m), 2.43 (1H, dd, J=16.6, 10.7 Hz), 2.70-2.90 (3H, m), 3.00-3.20 (6H, m), 3.50-3.90 (4H, br), 4.69 (1H, br), 6.90-7.10 (3H, m), 7.59 (1H, dd, J=8.8, 2.0 Hz), 7.75 (1H, dd, J=8.8, 2.0 Hz), 7.90-8.00 (3H, m), 8.30 (1H, s).

MS (FAB) m/z: 598 [(M+H)⁺, Cl³⁵], 600 [(M+H)⁺, Cl³⁷].

[0577]

[Referential Example 7]

(2RS)-2-(N-tert-Butoxycarbonylaminomethyl)-6-hydroxymethyl-1,2,3,4-tetrahydronaphthalene

In dichloromethane (10 ml), the (2RS)-2-(N-tert-butoxycarbonylaminomethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene (0.47 g) was dissolved. Aluminum

diisobutylhydride (a 0.95M hexane solution, 3.60 ml) was added dropwise to the resulting solution at an external temperature of -78°C , followed by stirring for 90 minutes without changing the temperature. Methanol was added to the reaction mixture and the mixture was heated to room temperature. The insoluble matter was filtered off from filtration through Celite. The filtrate was concentrated under reduced pressure. The concentrate was diluted with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby colorless crystals (0.31 g, 72%) was obtained. A portion of the resulting crystals was recrystallized from a mixed solvent of hexane and ethyl acetate, whereby colorless crystals were obtained.

[0578]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40-1.60 (1H, m), 1.46 (9H, s), 1.60-1.70 (1H, m), 1.90-2.00 (2H, m), 2.45 (1H, dd, $J=16.6, 10.7\text{Hz}$), 2.70-2.90 (3H, m), 3.10-3.30 (2H, m), 4.62 (2H, d, $J=5.9\text{Hz}$), 4.67 (1H, br), 7.00-7.20 (3H, m).

Elementary analysis for $\text{C}_{17}\text{H}_{25}\text{NO}_3$

Calculated: C, 70.07; H, 8.65; N, 4.81.

Found: C, 70.21; H, 8.49; N, 4.75.

[0579]

[Referential Example 8]

1-[[[(6RS)-6-(N-tert-Butoxycarbonylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (5 ml), the (2RS)-2-(N-tert-butoxycarbonylaminomethyl)-6-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (0.19 g) was dissolved. Pyridinium chlorochromate (0.17 g) was added to the resulting solution, followed by stirring at room temperature for 2 hours. The reaction mixture was purified as it was by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby a colorless solid (0.16 g) was obtained. The resulting solid was dissolved in dichloromethane (8 ml), followed by the addition of 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (0.24 g), triethylamine (80.0 μ l) and sodium triacetoxyboron hydride (0.17 g). The resulting mixture was stirred at room temperature for 16 hours under an argon gas atmosphere. An aqueous solution of sodium bicarbonate was added to the reaction mixture. The resulting mixture was diluted with dichloromethane and the organic layer was collected.. The organic layer was dried over sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby a colorless viscous liquid (0.33 g, 86%) was obtained.

[0580]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.30-1.50 (1H, m), 1.44 (9H, s), 1.80-2.00 (2H, m),

2.40 (1H, m), 2.51 (4H, br), 2.60-2.90 (3H, m), 3.09 (6H, br),
 3.39 (2H, s), 4.67 (1H, br), 6.90-7.00 (3H, m), 7.56 (1H, d, J=8.8Hz),
 7.77 (1H, d, J=8.8Hz), 7.80-8.00 (3H, m), 8.28 (1H, s).

MS (FAB) m/z: 584 [(M+H)⁺, Cl³⁵], 586 [(M+H)⁺, Cl³⁷].

[0581]

[Referential Example 9]

(2RS)-2-(tert-Butyldimethylsilyloxymethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene

In N,N-dimethylformamide (5 ml), (2RS)-2-hydroxymethyl-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene (1.71 g) was dissolved. To the resulting solution, imidazole (0.81 g) and tert-butyldimethylsilyl chloride (1.81 g) were added under ice cooling, followed by stirring at room temperature for 14 hours. After the addition of methanol, the mixture was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate, washed with water and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 50:1), whereby a pale yellow solid (2.20 g, 85%) was obtained.

[0582]

¹H-NMR (CDCl₃) δ: 0.06 (6H, s), 0.91 (9H, s), 1.40-1.60 (1H, m),
 1.90-2.10 (2H, m), 2.53 (1H, dd, J=17.1, 10.3Hz), 2.80-3.00 (3H, m),
 3.58 (2H, d, J=5.9Hz), 3.89 (3H, s), 7.14 (1H, d, J=7.8Hz), 7.70-
 7.80 (2H, m).

MS (FAB) m/z : 335 (M+H)⁺.

[0583]

[Referential Example 10]

(2RS)-2-(tert-Butyldimethylsilyloxymethyl)-6-hydroxymethyl-1,2,3,4-tetrahydronaphthalene

In the same manner as in Referential Example 7, the title compound was obtained using (2RS)-2-(tert-butyldimethylsilyloxymethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene as a raw material.

[0584]

¹H-NMR (CDCl₃) δ : 0.07 (6H, s), 0.91 (9H, s), 1.30-1.50 (1H, m), 1.50-1.60 (1H, m), 1.90-2.10 (2H, m), 2.48 (1H, m), 2.70-2.90 (3H, m), 3.58 (2H, m), 4.62 (2H, d, J=5.9 Hz), 7.09 (3H, m).

MS (FAB) m/z : 307 (M+H)⁺.

[0585]

[Referential Example 11]

(2RS)-6-(N-tert-Butoxycarbonylaminomethyl)-2-(tert-butyldimethylsilyloxymethyl)-1,2,3,4-tetrahydronaphthalene

In dichloromethane (10 ml), (2RS)-2-(tert-butyldimethylsilyloxymethyl)-6-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (1.00 g) was dissolved. Triethylamine (0.5 ml) was added to the resulting solution, followed by ice cooling. A solution of methanesulfonyl chloride (0.39 g) in dichloromethane (1 ml) was added to the reaction mixture and the mixture was stirred at room temperature for 9 hours. After washing with water, the reaction mixture was dried over

anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was treated in the same manner as in Referential Example 5, whereby the title compound (1.10 g, 83%) was obtained.

[0586]

$^1\text{H-NMR}$ (CDCl_3) δ : 0.06 (6H, s), 0.91 (9H, s), 1.40-1.60 (1H, m), 1.46 (9H, s), 1.90-2.00 (2H, m), 2.45 (1H, m), 2.70-2.90 (3H, m), 3.57 (2H, m), 4.24 (2H, m), 4.76 (1H, br), 7.00-7.10 (3H, m).

MS (FAB) m/z : 406 ($\text{M}+\text{H}$) $^+$.

[0587]

[Referential Example 12]

(2RS)-6-(N-tert-Butoxycarbonylaminomethyl)-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene

In tetrahydrofuran (10 ml), (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-2-(tert-butyldimethylsilyloxymethyl)-1,2,3,4-tetrahydronaphthalene (1.00 g) was dissolved. Tetrabutylammonium fluoride (a 1.0M tetrahydrofuran solution, 4.0 ml) was added to the resulting solution, followed by stirring at room temperature for 2 hours. After concentration under reduced pressure, the reaction mixture was diluted with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 to 2:1), whereby a colorless solid (0.77 g, 98%) was obtained. A portion of the solid was recrystallized from a

mixed solvent of hexane and ethyl acetate, whereby colorless crystals were obtained.

[0588]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40-1.60 (2H, m), 1.46 (9H, s), 1.90-2.10 (2H, m), 2.48 (1H, dd, $J=16.6, 10.7\text{Hz}$), 2.70-3.00 (3H, m), 3.6-3.7 (2H, m), 4.24 (2H, d, $J=5.4\text{Hz}$), 4.78 (1H, br), 7.00-7.10 (3H, m).

Elementary analysis for $\text{C}_{17}\text{H}_{25}\text{NO}_3$

Calculated: C, 70.07; H, 8.65; N, 4.81.

Found: C, 70.02; H, 8.61; N, 4.46.

[0589]

[Referential Example 13]

1-[[(2RS)-6-(N-tert-Butoxycarbonylaminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (5 ml), (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (0.17 g) was dissolved, followed by the addition of N-methylmorpholin N-oxide (0.13 g) and molecular sieves 4A (activated powder, 0.18 g). Under ice cooling, rutheniumtetrapropylammonium tetroxide (10 mg) was added and the mixture was stirred at room temperature for 1 hour. Diethyl ether was added to the reaction mixture. From the resulting mixture, insoluble matter was removed by filtration through Celite. The filtrate was distilled under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane) to yield the aldehyde compound. In the same

manner as in Referential Example 8, a reaction was effected using the resulting aldehyde compound, whereby the title compound (0.14 g, 41%) was obtained.

[0590]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.20-1.40 (1H, m), 1.44 (9H, s), 1.80-2.00 (2H, m), 2.20-2.40 (3H, m), 2.50-2.60 (4H, m), 2.60-2.80 (3H, m), 3.11 (4H, m), 4.20 (2H, d, $J=5.4\text{Hz}$), 4.79 (1H, br), 6.94 (3H, m), 7.57 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.79 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.90-8.00 (3H, m), 8.31 (1H, s).

MS (FAB) m/z : 584 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 586 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0591]

[Referential Example 14]

1-[[(2RS)-6-(N-tert-Butoxycarbonylaminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In carbon tetrachloride (2 ml), acetonitrile (2 ml) and water (3 ml), (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalen (0.21 g) was dissolved. To the resulting solution, sodium periodate (0.48 g) and ruthenium trichloride hydrate (4 mg) were added, followed by stirring for 90 minutes. The reaction mixture was diluted with dichloromethane. The organic layer thus separated was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was added with diethyl ether. After the filtration of insoluble matter, the filtrate was distilled under reduced pressure. The

carboxylic acid compound thus obtained was reacted in the same manner as in Referential Example 12, whereby the title compound (0.11 g, 25%) was obtained.

[0592]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (9H, s), 1.70-2.00 (2H, m), 2.60-2.90 (4H, m), 2.95 (1H, m), 3.11 (4H, m), 3.64 (2H, m), 3.76 (2H, m), 4.22 (2H, d, $J=5.4\text{Hz}$), 4.82 (1H, br), 6.90-7.10 (3H, m), 7.59 (1H, d, $J=8.8\text{Hz}$), 7.77 (1H, d, $J=8.8\text{Hz}$), 7.90-8.00 (3H, m), 8.31 (1H, s).

MS (FD) m/z : 597 (M^+ , Cl^{35}), 599 (M^+ , Cl^{37}).

[0593]

[Referential Example 15]

2-(N-tert-Butoxycarbonylaminomethyl)-7-methoxycarbonylnaphthalene

In the same manner as in Referential Example 11, a reaction was effected using 2-hydroxymethyl-7-methoxycarbonylnaphthalene (1.01 g) as a raw material, whereby the title compound was obtained.

[0594]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 3.98 (3H, s), 4.50 (2H, d, $J=5.4\text{Hz}$), 4.99 (1H, br), 7.53 (1H, d, $J=8.3\text{Hz}$), 7.80-7.90 (3H, m), 8.04 (1H, dd, $J=8.3, 1.0\text{Hz}$), 8.57 (1H, s).

Elementary analysis for $\text{C}_{18}\text{H}_{21}\text{NO}_4$

Calculated: C, 68.55; H, 6.71; N, 4.44.

Found: C, 68.54; H, 6.70; N, 4.46.

[0595]

[Referential Example 16]

1-[[7-(N-tert-Butoxycarbonylaminomethyl)naphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 6, a reaction was effected using 2-(N-tert-butoxycarbonylaminomethyl)-7-methoxycarbonylnaphthalene as a raw material, whereby the title compound was obtained.

[0596]

¹H-NMR (CDCl₃) δ: 1.46(9H,s), 3.12(4H,br), 3.50-4.00(4H,br), 4.45(2H,d,J=5.9Hz), 5.01(1H,br), 7.34(1H,d,J=7.8Hz), 7.45(1H,d,J=8.3Hz), 7.50-7.60(1H,m), 7.66(1H,s), 7.70-7.80(4H,m), 7.90-8.00(3H,m), 8.30(1H,s).

MS (FAB) m/z: 594 [(M+H)⁺, Cl³⁵], 596 [(M+H)⁺, Cl³⁷].

[0597]

[Referential Example 17]

1-[[7-(N-tert-Butoxycarbonylaminomethyl)naphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 7 or Referential Example 13, a reaction was effected using 2-(N-tert-butoxycarbonylaminomethyl)-7-methoxycarbonylnaphthalene as a raw material, whereby the title compound was obtained.

[0598]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 2.50-2.70 (4H, m), 3.10 (4H, br), 3.61 (2H, s), 4.44 (2H, d, $J=5.4\text{Hz}$), 4.92 (1H, br), 7.30-7.40 (2H, m), 7.50-7.70 (3H, m), 7.70-7.90 (3H, m), 7.90-8.00 (3H, m), 8.29 (1H, s).

MS (FAB) m/z : 580 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 582 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0599]

[Referential Example 18]

2-(N-tert-b-Butoxycarbonylaminomethyl)-6-methoxycarbonylnaphthalene

In a mixed solvent of tetrahydrofuran (40 ml) and methanol (8 ml), dimethyl 2,6-naphthalenedicarboxylate (2.00 g) was suspended. To the resulting suspension, sodium borohydride (0.98 g) was added under ice cooling, followed by stirring at room temperature for 21 hours. Water was added to the reaction mixture and the resulting mixture was concentrated under reduced pressure. Ethyl acetate and dilute hydrochloric acid were added to the residue and the organic layer was collected.. The organic layer was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was allowed to adsorb to silica gel (13 g), followed by purification by chromatography on silica gel column (hexane : ethyl acetate = 3:1), whereby colorless crystals (1.23 g, 70%) was obtained. The resulting crystals were reacted as in Referential Example 11, whereby the title compound was obtained.

[0600]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 3.98 (3H, s), 4.50 (2H, d, $J=5.4\text{Hz}$), 4.99 (1H, br), 7.47 (1H, d, $J=8.3\text{Hz}$), 7.75 (1H, s), 7.84 (1H, d, $J=8.8\text{Hz}$), 7.92 (1H, d, $J=8.8\text{Hz}$), 8.06 (1H, d, $J=8.3\text{Hz}$), 8.58 (1H, s).

Elementary analysis for $\text{C}_{18}\text{H}_{21}\text{NO}_4$

Calculated: C, 68.55; H, 6.71; N, 4.44.

Found: C, 68.93; H, 6.70; N, 4.29.

[0601]

[Referential Example 19]

Methyl 5-benzimidazolecarboxylate hydrochloride

Under ice cooling, thionyl chloride (2.30 ml) was added dropwise to methanol (50 ml). Then, 5-benzimidazolecarboxylic acid (5.00 g) was added, followed by heating under reflux for 5 hours. The reaction mixture was distilled under reduced pressure. The residue was pulverized in diethyl ether, followed by collection through filtration, whereby colorless crystals (6.36 g, 97%) was obtained.

[0602]

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 3.93 (3H, s), 7.96 (1H, d, $J=8.8\text{Hz}$), 8.12 (1H, d, $J=8.8\text{Hz}$), 8.40 (1H, s), 9.66 (1H, s).

Elementary analysis for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2 \cdot \text{HCl}$

Calculated: C, 50.84; H, 4.27; N, 13.17; Cl, 16.67.

Found: C, 50.64; H, 4.22; N, 13.12; Cl, 16.59.

[0603]

[Referential Example 20]

Methyl N-triphenylmethyl-5-benzimidazolecarboxylate

In dichloromethane (15 ml), methyl 5-benzimidazolecarboxylate hydrochloride (1.00 g) was suspended. To the resulting suspension, triethylamine (1.50 ml) and triphenylmethyl chloride (1.50 g) were added, followed by stirring at room temperature for 3 hours. The reaction mixture was diluted with dichloromethane, washed with water, and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby title compound (2.10 g, quant.) was obtained as a yellow solid.

[0604]

$^1\text{H-NMR}$ (CDCl_3) δ : 3.75 (2H, s), 3.89 (1H, s), 6.49 (1/3H, d, $J=8.8\text{Hz}$), 7.1-7.4 (16H, m), 7.61 (1/3H, dd, $J=8.8, 1.5\text{Hz}$), 7.78 (2/3H, d, $J=8.8\text{Hz}$), 7.87 (2/3H, dd, $J=8.8, 1.5\text{Hz}$), 7.96 (1/3H, s), 8.02 (2/3H, s).

MS (FAB) m/z : 419 ($\text{M}+\text{H}$) $^+$.

[0605]

[Referential Example 21]

Sodium thiazolo[5,4-c]pyridine-2-carboxylate

Ethyl thiazolo[5,4-c]pyridine-2-carboxylate (J. Heterocyclic Chem., 27, 563 (1990) (0.61 g) was dissolved in tetrahydrofuran (12 ml). To the resulting solution, a 1N aqueous sodium hydroxide solution (3 ml) was added, followed

by stirring at room temperature for 30 minutes. The insoluble matter was collected by filtration. Without purification, it was provided for the subsequent reaction as it was.

[0606]

¹H-NMR (DMSO-d₆) δ: 7.95 (1H, d, J=5.9Hz), 8.57 (1H, d, J=5.9Hz), 9.27 (1H, s).

[0607]

[Referential Example 22]

1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 8, the title compound was obtained using 5-tert-butoxycarbonyl-2-formyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 2.53-2.62 (4H, m), 2.72 (2H, br s), 3.10 (4H, br s), 3.59 (2H, s), 3.66 (2H, br s), 4.38 (2H, s), 6.54 (1H, s), 7.57 (1H, dd, J=8.8, 2.0Hz), 7.76 (1H, dd, J=8.8, 2.0Hz), 7.87-7.94 (3H, m), 8.29 (1H, s).

MS (FAB) m/z: 562 [(M+H)⁺, Cl³⁵], 564 [(M+H)⁺, Cl³⁷].

[0608]

[Referential Example 23]

3-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionic acid

Under ice cooling, sodium hydride (about 60% in oil, 126 mg) was added to tetrahydrofuran (10 ml). After stirring for 5 minutes, ethyl diethylphosphonoacetate (0.42 ml) was added dropwise and the resulting mixture was stirred for 30 minutes under ice cooling. To the reaction mixture, a solution of 5-tert-butoxycarbonyl-2-formyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (W094/21599) (360 mg) in tetrahydrofuran (10 ml) was added dropwise, followed by stirring for 1 hour under ice cooling. The reaction mixture was then concentrated under reduced pressure. Ethyl acetate was added to the concentrate. The mixture was washed with water and saturated saline and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 5:1), whereby a yellow oil (515 mg, quant) was obtained.

[0609]

The resulting oil (1.38 g, 4.09 mmol) was dissolved in methanol (40 ml), followed by the addition of 10% palladium carbon (0.20 g). The mixture was subjected to catalytic reduction for 1 hour under normal pressure. After the removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure, whereby pale yellow oil (1.41 g, quant.) was obtained.

[0610]

The oil (1.38 g, 4.07 mmol) was dissolved in tetrahydrofuran (15 ml), followed by the addition of ethanol (10 ml) and a 1N aqueous sodium hydroxide solution (8 ml). The resulting mixture was heated under reflux for 30 minutes. To the reaction mixture, 1N hydrochloric acid and ethyl acetate were added and the organic layer was collected.. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (1.28 g, quant.) was obtained as a colorless oil.

[0611]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 2.70 (2H, t, $J=7.3\text{Hz}$), 2.76 (2H, br s), 3.09 (2H, t, $J=7.3\text{Hz}$), 3.70 (2H, s), 4.40 (2H, s), 6.51 (1H, s).
MS (FD) m/z : 311 M^+ .

[0612]

[Referential Example 24]

(E)-3-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)acrylic acid

In the same manner as in Referential Example 23 except that hydrolysis was carried out instead of catalytic reduction, whereby the title compound was obtained.

[0613]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 2.85 (2H, br s), 3.73 (2H, br s), 4.47 (2H, s), 6.12 (1H, d, $J=15.4\text{Hz}$), 6.98 (1H, s), 7.77 (1H, d, $J=15.4\text{Hz}$).
MS (FD) m/z : 309 M^+ .

[0614]

[Referential Example 25]

1-(E)-3-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 6, a reaction was effected using (E)-3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)acrylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 2.80 (2H, br s), 3.12 (4H, t, J=4.9Hz), 3.46-3.86 (6H, m), 4.41 (2H, s), 6.39 (1H, d, J=15.1Hz), 6.83 (1H, s), 7.55-7.78 (3H, m), 7.89-7.92 (3H, m), 8.30 (1H, s).

MS (FD) m/z: 601 (M⁺, Cl³⁵), 603 (M⁺, Cl³⁷).

[0615]

[Referential Example 26]

1-[3-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (10 ml), 3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionic acid (445 mg) was dissolved, followed by the successive dropwise addition of N-methylmorpholine (170 μl) and isobutyl chloroformate (210 μl) at -20°C. After stirring at -20°C for 10 minutes, a solution of 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (607 mg) which had been

dissolved in dichloromethane (10 ml) was added. After stirring at -20°C for 10 minutes, the reaction mixture was heated to room temperature. The reaction mixture was concentrated under reduced pressure. The residue was then dissolved in dichloroethane. The resulting solution was washed with 1N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and saturated saline, dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1 to 2:1), whereby the title compound (625 mg, 72%) was obtained.

[0616]

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 2.53 (2H, t, J=7.5Hz), 2.68 (2H, br s), 2.99-3.10 (6H, m), 3.51-3.55 (2H, m), 3.64 (2H, br s), 3.72-3.77 (2H, m), 4.34 (2H, s), 6.43 (1H, s), 7.59 (1H, dd, J=8.8, 2.0Hz), 7.74 (1H, dd, J=8.8, 2.0Hz), 7.88-7.94 (3H, m), 8.30 (1H, s).
MS (FAB) m/z: 604 [(M+H)⁺, Cl³⁵], 606 [(M+H)⁺, Cl³⁷].

[0617]

[Referential Example 27]

3-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propanal

In dichloromethane (100 ml), ethyl 3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionate (1.68 g) obtained in Referential Example 102 was dissolved. After stirring at -78°C for 10 minutes, diisobutylaluminum hydride (a 0.98M hexane solution, 7.50 ml)

was slowly added dropwise. After stirring at -78°C for 10 minutes, methanol (50 ml) was added, followed by heating to room temperature. The reaction mixture was concentrated under reduced pressure. To the residue, dichloromethane and a saturated aqueous solution of ammonium chloride were added, followed by Celite filtration. The organic layer was separated from the filtrate, washed with saturated saline, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 5:1), whereby the title compound (935 mg, 55%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 2.76 (2H, br s), 2.81 (2H, t, $J=7.3\text{Hz}$), 3.09 (2H, t, $J=7.3\text{Hz}$), 3.69 (2H, br s), 4.39 (2H, s), 6.49 (1H, s), 9.81 (1H, s).

MS (FD) m/z : 295 M^+ .

[0618]

[Referential Example 28]

1-[3-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 8, a reaction was effected using 3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propanal and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0619]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.69-1.79 (2H, m),
 2.36 (2H, t, $J=7.3\text{Hz}$), 2.49-2.54 (4H, m), 2.65-2.75 (4H, m),
 3.10 (4H, br s), 3.67 (2H, br s), 4.37 (2H, s), 6.39 (1H, s),
 7.57 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.78 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.88-
 7.95 (3H, m), 8.30 (1H, s).

MS (FD) m/z : 589 (M^+ , Cl^{35}), 591 (M^+ , Cl^{37}).

[0620]

[Referential Example 29]

2-Aminomethyl-5-tert-butoxycarbonyl-4,5,6,7-
 tetrahydrothieno[3,2-c]pyridine

In tetrahydrofuran (100 ml), 5-tert-butoxycarbonyl-2-hydroxymethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (W094/21599) (2.10 g) was dissolved. After the addition of triphenylphosphine (2.66 g) and phthalimide (1.15 g), diethyl azodicarboxylate (1.28 ml) was added dropwise, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby a colorless solid was obtained. The resulting solid was dissolved in ethanol (40 ml), followed by the addition of hydrazine hydrate (0.39 ml). The resulting mixture was heated under reflux for 5 hours. The solid so precipitated was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane ~

dichloromethane : methanol = 25:1), whereby the title compound (448 mg, 21%) was obtained.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.42 (9H, s), 2.72 (2H, m), 3.60 (2H, m), 3.80 (2H, s), 4.32 (2H, s), 6.64 (1H, s).

MS (FD) m/z : 268 M^+ .

[0621]

[Referential Example 30]

1-[N-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]carbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (100 ml), 5-tert-butoxycarbonyl-2-aminomethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (150 mg) was dissolved. Under ice cooling, carbonyl diimidazole (136 mg) was added, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in toluene (50 ml). Under ice cooling, triethylamine (0.23 ml) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (356 mg) were added, followed by stirring overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water and saturated saline and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure and the residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 to 1:1), whereby the title compound (303 mg, 89%) was obtained.

[0622]

¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.70 (2H, br s), 3.07 (4H, t, J=4.9Hz), 3.48 (4H, t, J=4.9Hz), 3.66 (2H, br s), 4.36 (2H, br s), 4.39 (2H, d, J=5.4Hz), 4.69 (1H, t, J=5.4Hz), 6.58 (1H, s), 7.58 (1H, dd, J=8.8, 2.0Hz), 7.74 (1H, dd, J=8.8, 2.0Hz), 7.87-7.93 (3H, m), 8.30 (1H, s).

MS (FD) m/z: 604 (M⁺, Cl³⁵), 606 (M⁺, Cl³⁷).

[0623]

[Referential Example 31]

1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 6, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

[0624]

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 2.79 (2H, br s), 3.12 (4H, t, J=4.9Hz), 3.68 (2H, br s), 3.84 (4H, t, J=4.9Hz), 4.42 (2H, br s), 6.91 (1H, s), 7.59 (1H, dd, J=8.8, 2.0Hz), 7.75 (1H, dd, J=8.8, 2.0Hz), 7.90-7.97 (3H, m), 8.30 (1H, s).

MS (FD) m/z: 575 (M⁺, Cl³⁵), 577 (M⁺, Cl³⁷).

[0625]

[Referential Example 32]

1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine

In the same manner as in Referential Example 6, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-ethoxycarbonylpiperazine (WO96/10022) as raw materials.

[0626]

¹H-NMR (CDCl₃) δ: 1.32 (3H, t, J=7.3Hz), 1.47 (9H, s), 2.35-2.46 (1H, m), 2.55-2.64 (1H, m), 2.80 (2H, br s), 3.15-3.20 (1H, m), 3.69 (2H, br s), 3.75-3.85 (1H, m), 4.12 (2H, q, J=7.3Hz), 4.20-4.36 (2H, m), 4.39-4.48 (3H, m), 6.96 (1H, s), 7.59 (1H, dd, J=8.8, 2.0Hz), 7.75 (1H, dd, J=8.8, 2.0Hz), 7.88-7.94 (3H, m), 8.32 (1H, s).

MS (FAB) m/z: 648 [(M+H)⁺, Cl³⁵], 650 [(M+H)⁺, Cl³⁷].

[0627]

[Referential Example 33]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyano-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine

In ethanol, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (195 mg), triethylamine (0.2 ml) and sodium acetate (118 mg) were suspended. Cyan bromide (114 mg) was added to the resulting suspension, followed

by stirring at room temperature for 2 hours. To the residue obtained by concentration of the reaction mixture under reduced pressure, dichloromethane was added. The mixture was washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 100:1), whereby the title compound (51 mg, 28%) was obtained.

[0628]

¹H-NMR (CDCl₃) δ: 2.93-2.98 (2H, m), 3.11-3.14 (4H, m), 3.49-3.55 (2H, m), 3.81-3.84 (4H, m), 4.29 (2H, s), 6.89 (1H, s), 7.59 (1H, dd, J=8.8, 2.0 Hz), 7.75 (1H, dd, J=8.8, 2.0 Hz), 7.90-7.94 (3H, m), 8.30 (1H, s).

MS (FAB) m/z: 501 [(M+H)⁺, Cl³⁵], 503 [(M+H)⁺, Cl³⁷].

[0629]

[Referential Example 34]

1-[N-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In benzene (10 ml), 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (W094/21599) (283 mg) was dissolved. To the resulting solution, triethylamine (0.14 ml) and diphenylphosphoryl azide (0.21 mg) were added, followed by heating under reflux for 2 hours. After the reaction mixture was cooled to room temperature, 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (347

mg) and triethylamine (0.28 ml) were added and the mixture was heated under reflux overnight. After cooling to room temperature, the reaction mixture was added with dichloromethane and a 3N aqueous sodium hydroxide solution to extract the organic layer. The organic layer thus extracted was washed with 0.5N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and saturated saline, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 to 2:1), whereby the title compound (284 mg, 48%) was obtained.

[0630]

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.65 (2H, br s), 3.10 (4H, t, J=4.9Hz), 3.57 (4H, t, J=4.9Hz), 3.64 (2H, br s), 4.27 (2H, s), 6.15 (1H, br s), 7.58 (1H, dd, J=8.8, 2.0Hz), 7.73 (1H, dd, J=8.8, 2.0Hz), 7.87-7.93 (3H, m), 8.28 (1H, s).

MS (FAB) m/z: 591 [(M+H)⁺, Cl³⁵], 593 [(M+H)⁺, Cl³⁷].

[0631]

[Referential Example 35]

1-[N-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-N-methylcarbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In N,N-dimethylformamide (10 ml), 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]-4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine (147 mg) was dissolved. To the resulting solution, sodium hydride (60% in oil, 22 mg) was added, followed by stirring at room temperature for 30 minutes. After methyl iodide (0.023 ml) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 90 minutes, the residue obtained by the concentration of the reaction mixture under reduced pressure was added with ethyl acetate. The resulting mixture was washed with water and saturated saline and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (43 mg) was obtained.

[0632]

¹H-NMR (CDCl₃) δ: 1.49 (9H, s), 2.63 (2H, br s), 3.01 (4H, t, J=4.9Hz), 3.13 (3H, s), 3.40 (4H, t, J=4.9Hz), 3.67 (2H, br s), 4.31 (2H, s), 6.21 (1H, br s), 7.58 (1H, dd, J=8.8, 2.0Hz), 7.72 (1H, dd, J=8.8, 2.0Hz), 7.88-7.95 (3H, m), 8.27 (1H, s).
MS (FAB) m/z: 605 [(M+H)⁺, Cl³⁵], 607 [(M+H)⁺, Cl³⁷].

[0633]

[Referential Example 36]

1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 6, the title compound was obtained using 6-tert-butoxycarbonyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

[0634]

¹H-NMR (CDCl₃) δ: 1.47(9H,s), 2.84(2H,br s), 3.19(4H,br), 3.72(2H,t,J=5.4Hz), 3.87(2H,br s), 4.54(2H,s), 4.63(2H,br s), 7.57(1H,dd,J=8.8,2.0Hz), 7.76(1H,dd,J=8.8,2.0Hz), 7.87-7.94(3H,m), 8.30(1H,s).

MS (FAB) m/z: 577 [(M+H)⁺, Cl³⁵], 579 [(M+H)⁺, Cl³⁷].

[0635]

[Referential Example 37]

1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine

In N,N-dimethylformamide (30 ml), 6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (WO94/21599) (742 mg), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-ethoxycarbonylpiperazine hydrochloride (WO96/10022) (1.00 g) and benzotriazol-1-yl-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP(r)) (1.50 g) were dissolved. Triethylamine (0.40 ml) was added to the resulting solution, followed by stirring overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, ethyl acetate was added to the residue. The resulting mixture was washed with water and saturated saline and then, dried over anhydrous sodium

sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (505 mg, 30%) was obtained.

[0636]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24-1.37 (3H, m), 1.47 (9H, s), 2.45-2.60 (1H, m), 2.62-2.71 (1H, m), 2.75-2.90 (2H, m), 3.65-3.94 (3H, m), 4.19-4.31 (2H, m), 4.45-4.72 (4H, m), 5.35 (1/2H, br s), 5.71-5.77 (1/2H, m), 6.72 (1H, br s), 7.58 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.77 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.88-7.92 (3H, m), 8.33 (1H, s).
 MS (FAB) m/z : 649 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 651 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0637]

[Referential Example 38]

1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (5 ml), 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine (487 mg) was dissolved. Methanol (5 ml) and a 1N aqueous sodium hydroxide solution (3 ml) were added to the resulting solution, followed by stirring at room temperature for 4 hours. After the reaction mixture was adjusted to pH 1 to 2 by the addition of 1N hydrochloric acid, ethyl acetate was added and the organic layer was collected. After drying over anhydrous sodium sulfate, the residue

obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (5 ml). To the resulting solution, N-methylmorpholine (0.09 ml) and isobutyl chloroformate (0.11 ml) were added dropwise at -20°C . After stirring at -20°C for 10 minutes, an ammonia-dichloromethane solution (0.50 ml) was added to the reaction mixture. The resulting mixture was stirred at -20°C for 10 minutes, followed by the addition of ethanolic 1N hydrochloric acid (10 ml). The reaction mixture was heated to room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in dichloroethane. The resulting solution was washed with 1N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), whereby the title compound (317 mg, 68%) was obtained.

[0638]

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 1.41 (9H, s), 2.39-2.86 (4H, m), 3.60-3.80 (4H, m), 4.25-4.34 (1H, m), 4.36-4.34 (1/2H, m), 4.62 (2H, br s), 4.97 (1/2H, br s), 5.44-5.52 (1/2H, m), 6.19 (1/2H, br s), 7.30-7.39 (1H, m), 7.63-7.85 (3H, m), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.20-8.29 (2H, m), 8.48 (1H, s).

MS (FAB) m/z : 620 $[(M+H)^+, \text{Cl}^{35}]$, 622 $[(M+H)^+, \text{Cl}^{37}]$.

[0639]

[Referential Example 39]

1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(E)-4-chlorostyrylsulfonyl]piperazine

In the same manner as in Referential Example 6, the title compound was obtained using 6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as raw materials.

[0640]

¹H-NMR (CDCl₃) δ: 1.48(9H,s), 2.87(2H,br s), 3.31(4H,m), 3.75(2H,br s), 3.90(2H,br s), 4.57(2H,br s), 4.68(2H,s), 6.64(1H,d,J=15.6Hz), 7.28-7.35(5H,m).

MS (FAB) m/z: 553 [(M+H)⁺, Cl³⁵], 555 [(M+H)⁺, Cl³⁷].

[0641]

[Referential Example 40]

(3S)-3-Amino-1-tert-butoxycarbonylpyrrolidine

In the same manner as in Referential Example 5, a reaction was effected using (3R)-1-tert-butoxycarbonyl-3-methanesulfonyloxypyrrolidine (1.50 g), whereby the title compound was obtained.

[0642]

¹H-NMR (CDCl₃) δ: 1.46(9H,s), 1.98-2.11(2H,m), 2.95-3.10(1H,m), 3.26-3.60(4H,m).

MS (FAB) m/z: 187 (M+H)⁺.

[0643]

[Referential Example 41]

(3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamide]pyrrolidine
trifluoroacetate

In the same manner as in Referential Example 1, the title compound was obtained using (3S)-3-amino-1-tert-butoxycarbonylpyrrolidine as a raw material.

[0644]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.69-1.80 (1H,m), 1.88-1.99 (1H,m), 2.95-3.28 (4H,m), 3.75-3.84 (1H,m), 7.71 (1H,m), 7.91 (1H,m), 8.10-8.30 (4H,m), 8.53 (1H,s), 8.91 (1H,br s), 9.06 (1H,br s).

[0645]

[Referential Example 42]

(3S)-1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine

In the same manner as in Referential Example 8, a reaction was effected using 5-tert-butoxycarbonyl-2-formyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (WO94/21599) and (3S)-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine trifluoroacetate as raw materials, whereby the title compound was obtained.

[0646]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H,s), 1.52-1.63 (1H,m), 2.03-2.12 (1H,m), 2.19-2.27 (1H,m), 2.35-2.54 (2H,m), 2.73-2.85 (3H,m),

3.59 (1H, d, J=13.9Hz), 3.66 (1H, d, J=13.9Hz), 3.70 (2H, br s),
3.88-3.95 (1H, m), 4.39 (2H, s), 4.99 (1/2H, s), 5.02 (1/2H, s),
6.49 (1H, s), 7.55 (1H, dd, J=8.8, 2.0Hz), 7.82-7.90 (4H, m),
8.40 (1H, s).

MS (FD) m/z: 561 (M^+ , Cl³⁵), 563 (M^+ , Cl³⁷).

[0647]

[Referential Example 43]

(3S)-1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine

In the same manner as in Referential Example 6, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and (3S)-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine trifluoroacetate as raw materials.

[0648]

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 1.80-2.08 (2H, m), 2.75 (2H, br s),
3.48-3.87 (6H, m), 3.88-4.05 (1H, m), 4.37 (2H, br s), 6.09 (1H, br s),
7.05-7.15 (1H, m), 7.55 (1H, dd, J=8.8, 1.5Hz), 7.79-7.91 (4H, m),
8.41 (1H, s).

MS (FAB) m/z: 576 [(M+H)⁺, Cl³⁵], 578 [(M+H)⁺, Cl³⁷].

[0649]

[Referential Example 44]

(3S)-3-Amino-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In trifluoroacetic acid, (3R)-1-tert-butoxycarbonyl-3-methanesulfonyloxypryrrolidine was dissolved. After the resulting solution was concentrated under reduced pressure, diethyl ether was added to the concentrate, followed by the removal of the supernatant. The residue was reacted as in Referential Example 1, whereby the corresponding sulfonamide derivative was obtained as a crude product. The crude product was subjected to azide formation and reduction as in Referential Example 5, whereby the title compound was obtained.

[0650]

¹H-NMR (DMSO-d₆) δ: 1.38-1.53 (3H,m), 1.72-1.83 (1H,m), 2.81-2.89 (1H,m), 3.20-3.39 (4H,m), 7.69 (1H,dd,J=8.8,1.9Hz), 7.87 (1H,d,J=8.8Hz), 8.12 (1H,d,J=8.8Hz), 8.21 (1H,s), 8.26 (1H,d,J=8.8Hz), 8.39 (1H,s).

MS (FAB) m/z: 311 [(M+H)⁺, Cl³⁵], 313 [(M+H)⁺, Cl³⁷].

[0651]

[Referential Example 45]

(3S)-3-[[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]amino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In the same manner as in Referential Example 8, a reaction was effected using 5-tert-butoxycarbonyl-2-formyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (WO94/21599) and (3S)-3-amino-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine as raw materials, whereby the title compound was obtained.

[0652]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 1.60-1.69 (1H, m), 1.95-2.05 (1H, m), 2.72 (2H, br s), 3.11 (1H, dd, $J=10.3, 4.4\text{Hz}$), 3.30-3.46 (4H, m), 3.68 (2H, br s), 3.72 (2H, s), 4.36 (2H, s), 6.44 (1H, s), 7.56 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.86-7.91 (4H, m), 8.36 (1H, s).
 MS (FD) m/z : 561 (M^+ , Cl^{35}), 563 (M^+ , Cl^{37}).

[0653]

[Referential Example 46]

(3S)-3-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In the same manner as in Referential Example 6, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and (3S)-3-amino-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine as raw materials.

[0654]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 1.90-2.00 (1H, m), 2.11-2.22 (1H, m), 2.80 (2H, br s), 3.32-3.42 (1H, m), 3.44-3.57 (3H, m), 3.71 (2H, br s), 4.38 (2H, d, $J=1.5\text{Hz}$), 4.40-4.49 (1H, m), 5.80-5.87 (1H, m), 6.96 (1H, s), 7.54 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.83-7.89 (3H, m), 7.90 (1H, d, $J=8.8\text{Hz}$), 8.37 (1H, s).
 MS (FD) m/z : 576 [$(\text{M}+\text{H})^+$, Cl^{35}], 578 [$(\text{M}+\text{H})^+$, Cl^{37}].

[0655]

[Referential Example 47]

1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine

In the same manner as in Referential Example 6, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (W094/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride as raw materials.

[0656]

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 2.01 (2H, br s), 2.78 (2H, br s), 3.37-3.54 (4H, m), 3.68 (2H, br s), 3.78 (2H, t, J=6.1 Hz), 3.86 (2H, t, J=6.1 Hz), 4.39 (2H, s), 6.88 (1H, br s), 7.55 (1H, dd, J=8.8, 2.0 Hz), 7.75-7.80 (1H, m), 7.83-7.90 (3H, m), 8.33 (1H, s).

MS (FD) m/z: 589 (M⁺, Cl³⁵), 591 (M⁺, Cl³⁷).

[0657]

[Referential Example 48]

4-Benzylamino-1-tert-butoxycarbonylpiperidine

In dichloromethane (500 ml), 1-tert-butoxycarbonyl-4-piperidione (7.00 g) was dissolved, followed by the addition of benzylamine (4.03 ml) and sodium triacetoxyborohydride (11.91 g). The resulting mixture was stirred overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate. The resulting mixture was washed with water and saturated saline and then dried over anhydrous sodium sulfate. The solvent was

then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 1:1), whereby the title compound (7.46 g, 76%) was obtained.

[0658]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24-1.37 (2H,m), 1.45 (9H,s), 1.80-1.90 (2H,m), 2.62-2.70 (1H,m), 2.75-2.85 (1H,m), 2.98-3.07 (1H,m), 3.78-3.90 (3H,m), 3.95-4.10 (1H,m), 7.21-7.34 (5H,m).

MS (FD) m/z : 290 M^+ .

[0659]

[Referential Example 49]

4-Amino-1-tert-butoxycarbonylpiperidine acetate

In methanol (2 ml) and acetic acid (30 ml), 4-benzylamino-1-tert-butoxycarbonylpiperidine (4.04 g) was dissolved, followed by the addition of 10% palladium carbon (water content: about 50%, 3.06 g). The resulting mixture was subjected to catalytic reduction overnight under medium pressure (3 atmospheric pressure). After the removal of the catalyst by filtration, the filtrate was distilled off under reduced pressure. The residue was obtained was solidified in ethyl acetate, whereby the title compound (2.23 g, 57%) was obtained.

[0660]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.10-1.23 (2H,m), 1.39 (9H,s), 1.69-1.77 (2H,m), 1.80 (3H,s), 2.50 (2H,s), 2.67-2.88 (2H,m), 3.80-

3.90 (1H, m).

MS (FAB) m/z 201 (M+H)⁺.

Elementary analysis for C₁₀H₂₀N₂O₂·CH₃CO₂H

Calculated: C, 53.16; H, 9.37; N, 10.33.

Found: C, 53.51; H, 9.10; N, 9.93.

[0661]

[Referential Example 50]

4-[(6-Chloronaphthalen-2-yl)sulfonamido]piperidine
trifluoroacetate

In the same manner as in Referential Example 1, the title compound was obtained using 4-amino-1-tert-butoxycarbonylpiperidine hydrochloride and 6-chloro-2-naphthylsulfonyl chloride as raw materials.

[0662]

¹H-NMR (DMSO-d₆) δ: 1.47-1.60 (2H, m), 1.68-1.78 (2H, m), 2.81-2.95 (2H, m), 3.10-3.20 (2H, m), 3.29-3.40 (1H, m), 7.70 (1H, dd, J=8.8, 2.0 Hz), 7.91 (1H, dd, J=8.8, 2.0 Hz), 8.11-8.15 (2H, m), 8.21 (1H, s), 8.31 (1H, br s), 8.50 (1H, s), 8.55 (1H, br s).

MS (FAB) m/z : 325 [(M+H)⁺, Cl³⁵], 327 [(M+H)⁺, Cl³⁷].

[0663]

[Referential Example 51]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-cyanobenzofuran-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 6, a reaction

was effected using 6-cyanobenzofuran-2-carboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0664]

$^1\text{H-NMR}$ (CDCl_3) δ : 3.21 (4H, s), 3.95 (4H, s), 7.32 (1H, d, $J=1.0\text{Hz}$), 7.55 (1H, dd, $J=8.3, 1.0\text{Hz}$), 7.59 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.72 (1H, d, $J=8.3\text{Hz}$), 7.77 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.81 (1H, s), 7.88-7.95 (3H, m), 8.32 (1H, s).

MS (FAB) m/z : 480 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 482 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0665]

[Referential Example 52]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyanobenzothiophen-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 6, a reaction was effected using 5-cyanobenzothiophene-2-carboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0666]

$^1\text{H-NMR}$ (CDCl_3) δ : 3.18 (4H, s), 3.89 (4H, s), 7.43 (1H, d, $J=2.0\text{Hz}$), 7.60 (1H, d, $J=8.8\text{Hz}$), 7.73-7.80 (2H, m), 7.85-7.95 (4H, m), 8.10 (1H, s), 8.32 (1H, s).

MS (FAB) m/z : 496 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 498 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0667]

[Referential Example 53]

6-Methoxy-3,4-dihydroisoquinoline

In tetrahydrofuran (100 ml), 3-methoxyphenethylamine (75.0 g) was dissolved. To the resulting solution, formic acid (60 ml) and acetic anhydride (108 ml) were added under ice cooling, followed by stirring overnight at room temperature. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture and the organic layer was collected. The organic layer was washed with saturated saline and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in benzene (200 ml), followed by the dropwise addition of phosphorus oxychloride (140 ml) under ice cooling. After stirring at 70°C for 15 minutes, the reaction mixture was successively added with ice and 2N hydrochloric acid. The resulting mixture was stirred for 1 hour under ice cooling. The water layer was separated from the reaction mixture, neutralized with potassium carbonate and then extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), whereby the title compound (13.5 g, 17%) was obtained.

[0668]

¹H-NMR (CDCl₃) δ: 2.72 (2H, t, J=7.3Hz), 3.72 (2H, t, J=7.3Hz),

3.83 (3H, s), 6.68 (1H, d, J=2.4Hz), 6.79 (1H, dd, J=8.3, 2.4Hz),
7.22 (1H, d, J=8.3Hz), 8.25 (1H, s).

MS (FAB) m/z: 162 (M+H)⁺.

[0669]

[Referential Example 54]

6-Methoxy-1,2,3,4-tetrahydroisoquinoline

In methanol (100 ml), 6-methoxy-3,4-dihydroisoquinoline (10.4 g) was dissolved. To the resulting solution, water (10 ml) and then sodium borohydride (6.10 g) were added. The resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane, followed by washing with water. The organic layer thus separated was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:15), whereby the title compound (7.95 g, 76%) was obtained.

[0670]

¹H-NMR (CDCl₃) δ: 2.79 (2H, t, J=5.9Hz), 3.12 (2H, t, J=5.9Hz),
3.76 (3H, s), 3.96 (2H, s), 6.62 (1H, s), 6.70 (1H, dd, J=8.3, 2.4Hz),
6.92 (1H, d, J=8.3Hz).

MS (FAB) m/z: 164 (M+H)⁺.

[0671]

[Referential Example 55]

6-Hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride

In dimethyl sulfide (20 ml), 6-methoxy-1,2,3,4-tetrahydroisoquinoline (7.75 g) was dissolved. Under ice cooling, aluminum chloride (19.0 g) was added to the resulting solution, followed by stirring at room temperature for 3 hours. Dichloromethane and dilute hydrochloric acid were added to separate the water layer. The water layer was made acidic by the addition of a saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in saturated ethanol hydrochloride (100 ml). To the residue obtained by distilling off the solvent under reduced pressure, ethyl acetate was added. The solid thus precipitated was collected by filtration, whereby the title compound (7.91 g, 90%) was obtained.

[0672]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.06 (2H, t, $J=5.9\text{Hz}$), 3.43 (2H, m), 4.25 (2H, s), 6.76 (1H, d, $J=2.0\text{Hz}$), 6.83 (1H, dd, $J=8.3, 2.0\text{Hz}$), 7.15 (1H, d, $J=8.3\text{Hz}$), 9.71 (3H, br s).

MS (FAB) m/z : 150 ($\text{M}+\text{H}$) $^+$.

[0673]

[Referential Example 56]

2-tert-Butoxycarbonyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline

In methanol (100 ml), 6-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (7.87 g) was dissolved. To the resulting solution, triethylamine (4.67 ml) and di-tert-butyl dicarbonate (13.95 g) were added, followed by stirring at room temperature for 3 hours. Ethyl acetate was added to the residue obtained by concentration of the reaction mixture under reduced pressure. The resulting mixture was washed with 1N hydrochloric acid, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 10:1 to 3:1), whereby the title compound (9.96 g, 94%) was obtained.

[0674]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 2.75 (2H, t, $J=5.9\text{Hz}$), 3.61 (2H, t, $J=5.9\text{Hz}$), 4.48 (2H, s), 6.25 (1H, br s), 6.64 (1H, d, $J=2.4\text{Hz}$), 6.70 (1H, br s), 6.93 (1H, d, $J=7.8\text{Hz}$).

[0675]

[Referential Example 57]

2-tert-Butoxycarbonyl-6-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydroisoquinoline

In pyridine (100 ml), 2-tert-butoxycarbonyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (9.96 g) was dissolved. To the resulting solution, trifluorosulfonic anhydride (8.10 ml) was added dropwise under ice cooling, followed by stirring at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure and the residue was

purified by chromatography on a silica gel column (hexane : ethyl acetate = 10:1 to 61), whereby the title compound (13.47 g, 88%) was obtained as a colorless solid.

[0676]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 2.87 (2H, t, $J=5.9\text{Hz}$), 3.66 (2H, t, $J=5.9\text{Hz}$), 4.59 (2H, s), 7.06 (1H, br s), 7.08 (1H, d, $J=8.3\text{Hz}$), 7.17 (1H, d, $J=8.3\text{Hz}$).

Elementary analysis for $\text{C}_{15}\text{H}_{18}\text{F}_3\text{NO}_5\text{S}$

Calculated: C, 47.24; H, 4.76; F, 14.94; N, 3.67; S, 8.41.

Found: C, 47.34; H, 4.72; F, 15.25; N, 3.42; S, 8.65.

[0677]

[Referential Example 58]

2-tert-Butoxycarbonyl-6-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline

In methanol (50 ml), 2-tert-butoxycarbonyl-6-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydroisoquinoline (1.34 g) was dissolved, followed by the addition of triethylamine (0.73 ml), palladium (II) acetate (40 mg) and 1,3-(diphenylphosphino)propane (145 mg). Under a carbon monoxide gas stream, the resulting mixture was stirred overnight at 70°C . The reaction mixture was concentrated under reduce pressure and the residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 15:1), whereby the title compound (665 mg, 65%) was obtained.

[0678]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (9H, s), 2.88 (2H, m), 3.66 (2H, br s), 3.91 (3H, s), 4.62 (2H, s), 7.17 (1H, d, $J=7.8\text{Hz}$), 7.83 (1H, s), 7.84 (1H, d, $J=7.8\text{Hz}$).

[0679]

[Referential Example 59]

1-[(2-tert-Butoxycarbonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 6, the title compound was obtained using 2-tert-butoxycarbonyl-6-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

[0680]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 2.76 (2H, t, $J=5.4\text{Hz}$), 3.09 (4H, br), 3.60 (2H, t, $J=5.4\text{Hz}$), 3.77 (4H, br), 4.52 (2H, s), 7.12-7.25 (3H, m), 7.59 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.75 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.88-7.95 (3H, m), 8.30 (1H, s).

MS (FAB) m/z : 570 [$(\text{M}+\text{H})^+$, Cl^{35}], 572 [$(\text{M}+\text{H})^+$, Cl^{37}].

[0681]

[Referential Example 60]

(3RS)-3-Amino-1-tert-butoxycarbonylpyrrolidine

In methanol (30 ml), 3-aminopyrrolidine (0.54 g) was dissolved under ice cooling, followed by the addition of diisopropylethylamine (720 μl) and 2-(tert-

butoxycarbonyloxyimino)-2-phenylacetonitrile (0.84 g). The resulting mixture was gradually heated to room temperature and stirred for 11 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ 5% methanol - dichloromethane), whereby the title compound (0.59 g, 94%) was obtained.

[0682]

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.0-2.3 (2H, m), 3.1-4.0 (5H, m).

[0683]

[Referential Example 61]

(3RS)-1-tert-Butoxycarbonyl-3-[(6-chloronaphthalen-2-yl)sulfonamide]pyrrolidine

In the same manner as in Referential Example 1, the title compound was obtained using (3RS)-3-amino-1-tert-butoxycarbonylpyrrolidine as a raw material.

[0684]

¹H-NMR (CDCl₃) δ: 1.37 (9H, s), 1.60-2.10 (2H, m), 3.00-3.50 (4H, m), 3.88 (1H, br), 4.96 (1H, br), 7.50-7.60 (1H, m), 7.80-7.90 (4H, m), 8.43 (1H, s).

MS (FAB) m/z: 411 [(M+H)⁺, Cl³⁵], 413 [(M+H)⁺, Cl³⁷].

[0685]

[Referential Example 62]

1,4-Dibenzyl-2-methoxycarbonylmethylpiperazine

In toluene (250 ml), N,N'-dibenzylethylenediamine (12 ml)

and triethylamine (12 ml) were dissolved, followed by the dropwise addition of methyl 3-bromocrotonate (7.0 ml) under ice cooling. The resulting mixture was stirred at room temperature for 24 hours. After the addition of triethylamine (2.0 ml), the resulting mixture was stirred at room temperature for 71 hours. The insoluble matter was filtered off and the filtrate was distilled under reduced pressure. The residue was added with 10% hydrochloric acid (300 ml) and crystals so precipitated were removed by filtration. Ethyl acetate was added to the filtrate. Potassium carbonate was added to the water layer so separated to make it alkaline. Ethyl acetate was added to the resulting mixture. The organic layer so separated was washed with saturated saline and dried over anhydrous potassium carbonate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (1.07 g, 62%) was obtained.

[0686]

$^1\text{H-NMR}$ (CDCl_3) δ : 2.30-2.70 (8H, m), 3.11 (1H, br s), 3.40-3.80 (4H, m), 3.60 (3H, s), 7.20-7.40 (10H, m).
MS (FAB) m/z : 339 ($\text{M}+\text{H}$) $^+$.

[0687]

[Referential Example 63]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-methoxycarbonylmethylpiperazine

In acetic acid (40 ml), 1,4-dibenzyl-2-

methoxycarbonylmethylpiperazine (2.04 g) was dissolved, followed by the addition of 10% palladium carbon (water content: about 50%, 2.00 g). The resulting mixture was subjected to catalytic reduction at room temperature for 4 hours under 4 atmospheric pressure. After removal of the catalyst by filtration, the residue obtained by distilling the filtrate under reduced pressure was added with dichloromethane and a saturated aqueous solution of potassium carbonate. The insoluble matter so precipitated was filtered off. The organic layer so separated was washed with saturated saline and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was dissolved in dichloromethane (30 ml), followed by the addition of 6-chloro-2-naphthylsulfonyl chloride (782 mg). The resulting mixture was stirred at 0°C for 2 hours. To the reaction mixture, triethylamine (410 μ l) was added, followed by stirring at 0°C for further three hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ 3% methanol - dichloromethane), whereby the title compound (759 mg, 33%) was obtained.

[0688]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.71 (1H, br s), 2.15-2.55 (4H, m), 2.90-3.05 (2H, m), 3.15-3.25 (1H, m), 3.60-3.70 (5H, m), 7.55-7.60 (1H, m), 7.75-7.80 (1H, m), 7.85-7.95 (3H, m), 8.30 (1H, s).

MS (FAB) m/z : 383 $[(M+H)^+, Cl^{35}]$, 385 $[(M+H)^+, Cl^{37}]$.

[0689]

[Referential Example 64]

1-Benzenesulfonyl-6-chloroindole

At -78°C , *n*-butyl lithium (a 1.61M hexane solution, 3.34 ml) was added to a solution of 6-chloroindole (777 mg) in tetrahydrofuran (25 ml), followed by heating to -40°C over 1 hour. The reaction mixture was cooled back to -78°C and added with benzenesulfonyl chloride (867 μl). The resulting mixture was heated to room temperature over 3 hours. Water was added to the reaction mixture, followed by extraction with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (40 g of silica gel, hexane : ethyl acetate = 5:7). The white solid so obtained was recrystallized from ethanol, whereby the title compound (826 mg, 55%) was obtained as a white solid.

[0690]

$^1\text{H-NMR}$ (CDCl_3) δ : 6.64 (1H, d, $J=3.9\text{Hz}$), 7.21 (1H, dd, $J=8.3, 1.2\text{Hz}$), 7.42-7.60 (5H, m), 7.88 (2H, d, $J=7.3\text{Hz}$), 8.03 (1H, s).

Elementary analysis for $\text{C}_{14}\text{H}_{10}\text{ClNO}_2\text{S}$

Calculated: C, 57.63; H, 3.45; Cl, 12.15; N, 4.80; S, 10.99.

Found: C, 57.48; H, 3.75; Cl, 12.34; N, 4.87;

S, 10.87.

[0691]

In the same manner as in Referential Example 64, the compounds which will be described below in Referential Examples 65 and 66 were synthesized.

[0692]

[Referential Example 65]

1-Benzenesulfonyl-5-chloroindole

[0693]

$^1\text{H-NMR}$ (CDCl_3) δ : 6.61 (1H, d, $J=3.9\text{Hz}$), 7.26 (1H, dd, $J=8.3, 2.0\text{Hz}$), 7.45 (2H, t, $J=7.3\text{Hz}$), 7.50 (1H, d, $J=2.0\text{Hz}$), 7.56 (1H, m), 7.59 (1H, d, $J=3.9\text{Hz}$), 7.86 (2H, m), 7.92 (1H, d, $J=8.3\text{Hz}$).

Elementary analysis for $\text{C}_{14}\text{H}_{10}\text{ClNO}_2\text{S}$

Calculated: C, 57.63; H, 3.45; Cl, 12.15; N, 4.80;

S, 10.99.

Found: C, 57.82; H, 3.58; Cl, 11.91; N, 4.79;

S, 10.92.

[0694]

[Referential Example 66]

1-Benzenesulfonyl-5-bromoindole

[0695]

$^1\text{H-NMR}$ (CDCl_3) δ : 6.60 (1H, d, $J=3.7\text{Hz}$), 7.42 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.45 (2H, t, $J=8.8\text{Hz}$), 7.55 (1H, d, $J=8.8\text{Hz}$), 7.57 (1H, d, $J=3.7\text{Hz}$), 7.73 (1H, d, $J=2.0\text{Hz}$), 7.86 (2H, d, $J=8.8\text{Hz}$), 7.87 (1H, d, $J=8.8\text{Hz}$).

Elementary analysis for $\text{C}_{14}\text{H}_{10}\text{BrNO}_2\text{S}$

Calculated: C, 50.01; H, 3.00; N, 4.17; Br, 23.77; S, 9.54.

Found: C, 49.96; H, 2.97; N, 4.02; Br, 23.90; S, 9.53.

[0696]

[Referential Example 67]

1-Benzenesulfonyl-5-trimethylsilylethynylindole

In tetrahydrofuran (7.00 ml), 1-benzenesulfonyl-5-bromoindole (1.50 g) and triphenylphosphine (351 mg) were dissolved. Triethylamine (20 ml), N,N-dimethylformamide (7.00 ml), trimethylsilylacetylene (945 μ l) and palladium acetate (100 mg) were added to the resulting solution at room temperature, followed by heating under reflux for 5 hours. After the reaction mixture was allowed to cool down to room temperature, ethyl acetate and water were added to the reaction mixture and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 20:1 to 10:1), whereby the title compound (935 mg, 59%) was obtained as a white solid.

[0697]

$^1\text{H-NMR}$ (CDCl_3) δ : 0.24 (9H, s), 6.62 (1H, d, $J=3.9\text{Hz}$), 7.42 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.44 (2H, t, $J=7.8\text{Hz}$), 7.52 (1H, d, $J=7.8\text{Hz}$), 7.56 (1H, d, $J=3.9\text{Hz}$), 7.66 (1H, d, $J=1.5\text{Hz}$), 7.85 (2H, d, $J=7.8\text{Hz}$), 7.92 (1H, d, $J=8.8\text{Hz}$).

MS (FAB) m/z : 354 ($\text{M}+\text{H}$) $^+$

[0698]

[Referential Example 68]

5-Chloro-1-ethylindole

In benzene (10 ml), 5-chloroindole (1.52 g) was dissolved, followed by the addition of a 50% aqueous solution of sodium hydroxide (10 ml), tetrabutylammonium bromide (161 mg) and bromoethane (1.64 g). The resulting mixture was stirred at room temperature for 40 hours. After the addition of a saturated aqueous solution of ammonium chloride to the reaction mixture, water and dichloromethane were added and the organic layer was collected. After the organic layer was dried over anhydrous sodium sulfate, the residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:20), whereby the title compound (1.68 g, 93%) was obtained as colorless crystals.

[0699]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (3H, t, $J=7.3\text{Hz}$), 4.16 (2H, q, $J=7.3\text{Hz}$), 6.43 (1H, d, $J=2.4\text{Hz}$), 7.14 (1H, d, $J=2.4\text{Hz}$), 7.15 (1H, d, $J=8.3\text{Hz}$), 7.26 (1H, $J=8.3\text{Hz}$), 7.59 (1H, s).

MS (EI) m/z : 179 (M^+ , Cl^{35}), 181 (M^+ , Cl^{37}).

[0700]

[Referential Example 69]

1-Benzenesulfonyl-6-chloroindole-2-sulfonyl chloride

After the dropwise addition of tert-butyl lithium (a 1.56M pentane solution, 1.78 ml) to a solution of 1-

benzenesulfonyl-6-chloroindole (777 mg) in ether (12 ml) at -78°C , the mixture was heated to 0°C over 30 minutes. The reaction mixture was stirred for 1 hour and then cooled back to -78°C . A sulfurous acid gas was then introduced into the reaction mixture. After heating to room temperature over 1 hour, stirring was conducted for 1 hour. The reaction mixture was concentrated under reduced pressure. Hexane was added to the concentrate, followed by concentration under reduced pressure again. The residue was dissolved in dichloromethane. To the resulting solution, N-chlorosuccinimide (390 mg) was added at 0°C , followed by heating over 1 hour to room temperature. Stirring was then conducted for 30 minutes. Dichloromethane and water were added to the reaction mixture and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was recrystallized from methanol, whereby the title compound (857 mg, 79%) was obtained as a white solid.

[0701]

$^1\text{H-NMR}$ (CDCl_3) δ : 7.39 (1H, dd, $J=8.3, 1.6\text{Hz}$), 7.48–7.67 (4H, m), 7.68 (1H, s), 8.08 (2H, d, $J=7.3\text{Hz}$), 8.35 (1H, s).

Elementary analysis for $\text{C}_{14}\text{H}_9\text{ClNO}_4\text{S}_2$

Calculated: C, 43.09; H, 2.32; Cl, 18.17; N, 3.59; S, 16.43.

Found: C, 43.32; H, 2.67; Cl, 18.25; N, 3.64; S, 16.22.

[0702]

In the same manner as in Referential Example 69, compounds which will be described below in Referential Examples 70 to 77 were synthesized.

[0703]

[Referential Example 70]

1-Benzenesulfonylindole-2-sulfonyl chloride

[0704]

$^1\text{H-NMR}$ (CDCl_3) δ : 7.40 (1H, t, $J=7.6\text{Hz}$), 7.45-7.53 (2H, m), 7.57-7.67 (2H, m), 7.69 (1H, d, $J=7.8\text{Hz}$), 7.73 (1H, s), 8.08 (2H, d, $J=7.3\text{Hz}$), 8.31 (1H, d, $J=8.8\text{Hz}$).

MS (EI) m/z : 355 M^+ .

Elementary analysis for $\text{C}_{14}\text{H}_{10}\text{ClNO}_4\text{S}_2$

Calculated: C, 47.26; H, 2.83; Cl, 9.96; N, 3.94; S, 18.02.

Found: C, 47.33; H, 3.08; Cl, 10.04; N, 3.98; S, 18.18.

[0705]

[Referential Example 71]

1-Benzenesulfonyl-5-chloroindole-2-sulfonyl chloride

[0706]

$^1\text{H-NMR}$ (CDCl_3) δ : 7.46-7.54 (2H, m), 7.58 (1H, dd, $J=9.3, 2.0\text{Hz}$), 7.63 (1H, t, $J=7.3\text{Hz}$), 7.64 (1H, s), 7.67 (1H, d, $J=2.0\text{Hz}$), 8.06 (2H, d, $J=7.3\text{Hz}$), 8.26 (1H, d, $J=9.3\text{Hz}$).

MS (EI) m/z : 291 (M^+ , Cl^{35}), 293 (M^+ , Cl^{37}).

Elementary analysis for $\text{C}_{14}\text{H}_9\text{Cl}_2\text{NO}_4\text{S}_2$

Calculated: C, 43.09; H, 2.32; Cl, 18.27; N, 3.59; S, 16.43.

Found: C, 42.98; H, 2.51; Cl, 18.36; N, 3.59 S, 16.47.

[0707]

[Referential Example 72]

5-Chloro-1-ethylindole-2-sulfonyl chloride

[0708]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.52 (3H, t, $J=7.3\text{Hz}$), 4.59 (2H, q, $J=7.3\text{Hz}$), 7.36 (1H, s), 7.39 (1H, d, $J=8.8\text{Hz}$), 7.45 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.73 (1H, d, $J=2.0\text{Hz}$).

MS (EI) m/z : 277 [M^+ , Cl^{35}], 279 [M^+ , Cl^{37}]

[0709]

[Referential Example 73]

1-Benzenesulfonyl-5-trimethylsilylethynylindole-2-sulfonyl chloride

[0710]

$^1\text{H-NMR}$ (CDCl_3) δ : 0.26 (9H, s), 7.48 (2H, t, $J=7.8\text{Hz}$), 6.61 (1H, t, $J=7.8\text{Hz}$), 7.65 (1H, s), 7.69 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.79 (1H, d, $J=1.5\text{Hz}$), 8.04 (2H, d, $J=7.8\text{Hz}$), 8.24 (1H, d, $J=8.8\text{Hz}$).

MS (FAB) m/z : 452 [$(\text{M}+\text{H})^+$, Cl^{35}], 454 [$(\text{M}+\text{H})^+$, Cl^{37}]

[0711]

[Referential Example 74]

5-Chlorobenzo[b]furan-2-sulfonyl chloride

[0712]

$^1\text{H-NMR}$ (CDCl_3) δ : 7.57 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.59 (1H, s), 7.61 (1H, d, $J=8.8\text{Hz}$), 7.76 (1H, d, $J=2.0\text{Hz}$).

MS (EI) m/z : 250 (M^+ , Cl^{35}), 252 (M^+ , Cl^{37}).

Elementary analysis for $\text{C}_8\text{H}_4\text{Cl}_2\text{O}_3\text{S}$

Calculated: C, 38.27; H, 1.61; Cl, 28.24; S, 12.77.

Found: C, 38.33; H, 1.71; Cl, 28.16; S, 12.57.

[0713]

[Referential Example 75]

6-Chlorobenzo[b]furan-2-sulfonyl chloride

[0714]

$^1\text{H-NMR}$ (CDCl_3) δ : 7.43 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.62 (1H, s),
7.69 (1H, s), 7.70 (1H, d, $J=8.8\text{Hz}$).

MS (EI) m/z : 250 (M^+ , Cl^{35}), 252 (M^+ , Cl^{37}).

Elementary analysis for $\text{C}_8\text{H}_4\text{Cl}_2\text{O}_3\text{S}$

Calculated: C, 38.27; H, 1.61; Cl, 28.24; S, 12.77.

Found: C, 38.31; H, 1.60; Cl, 28.34; S, 12.60.

[0715]

[Referential Example 76]

5-Chlorobenzo[b]thiophene-2-sulfonyl chloride

[0716]

$^1\text{H-NMR}$ (CDCl_3) δ : 7.57 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.85 (1H, d, $J=8.8\text{Hz}$),
7.96 (1H, d, $J=2.0\text{Hz}$), 8.08 (1H, s).

MS (FD) m/z : 266 (M^+ , Cl^{35}), 268 (M^+ , Cl^{37}).

[0717]

[Referential Example 77]

6-Chlorobenzo[b]thiophene-2-sulfonyl chloride

[0718]

$^1\text{H-NMR}$ (CDCl_3) δ : 7.51 (1H, dd, $J=8.3, 1.5\text{Hz}$), 7.90 (1H, d, $J=8.3\text{Hz}$),
7.92 (1H, s), 8.11 (1H, s).

MS (FAB) m/z: 266 [(M+H)⁺, Cl³⁵], 268 [(M+H)⁺, Cl³⁷].

[0719]

[Referential Example 78]

1-tert-Butoxycarbonyl-4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine

To a solution of 1-benzenesulfonyl-5-chloroindole-2-sulfonyl chloride (4.41 g) in dichloromethane (75 ml), tert-butyl-1-piperazine carboxylate (2.21 g) and triethylamine (1.65 ml) were added under ice cooling. The resulting mixture was stirred at room temperature for 3 hours. After completion of the reaction, water and dichloromethane were added to the reaction mixture. The organic layer so separated was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : n-hexane = 1:20), whereby the title compound (3.63 g, 60%) was obtained as colorless crystals.

[0720]

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 3.35-3.42 (4H, br), 3.50-3.55 (4H, br), 7.40-7.48 (4H, m), 7.53-7.58 (2H, m), 8.00-8.05 (2H, m), 8.23 (1H, d, J=8.8 Hz).

[0721]

In the same manner as in Referential Example 78, compounds which will be described below in Referential Examples 79 to 82 were synthesized.

[0722]

[Referential Example 79]

1-tert-Butoxycarbonyl-4-[(1-benzenesulfonylindol-2-yl)sulfonyl]piperazine

[0723]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (9H, s), 3.34-3.44 (4H, br), 3.48-3.56 (4H, br), 7.33 (1H, t, $J=7.3\text{Hz}$), 7.36-7.45 (2H, m), 7.47-7.61 (4H, m), 8.04 (2H, d, $J=7.3\text{Hz}$), 8.29 (1H, d, $J=8.8\text{Hz}$).

MS (EI) m/z : 505 M^+ .

[0724]

[Referential Example 80]

1-tert-Butoxycarbonyl-4-[(5-chloro-1-ethylindol-2-yl)sulfonyl]piperazine

[0725]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (3H, t, $J=7.3\text{Hz}$), 1.43 (9H, s), 3.16-3.23 (4H, m), 3.48-3.55 (4H, m), 4.45 (2H, q, $J=7.3\text{Hz}$), 7.03 (1H, s), 7.32-7.34 (2H, m), 7.66 (1H, d, $J=2.0\text{Hz}$).

MS (EI) m/z : 427 (M^+ , Cl^{35}), 429 (M^+ , Cl^{37}).

[0726]

[Referential Example 81]

1-tert-Butoxycarbonyl-4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]homopiperazine

[0727]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.98-2.17 (2H, m), 3.42-3.57 (8H, m), 7.28 (1H, s), 7.41-7.46 (3H, m), 7.53-7.57 (2H, m),

8.05 (2H, d, J=7.3Hz), 8.20 (1H, d, J=9.3Hz).

MS (FAB) m/z: 554 [(M+H)⁺, Cl³⁵], 556 [(M+H)⁺, Cl³⁷].

[0728]

[Referential Example 82]

cis-1-[(1-Benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]-3,5-dimethylpiperazine

[0729]

¹H-NMR (CDCl₃) δ: 1.07 (6H, d, J=6.4Hz), 2.45-2.55 (2H, m), 2.95-3.05 (2H, m), 3.75-3.80 (2H, m), 7.35-7.50 (4H, m), 7.50-7.60 (2H, m), 8.00-8.05 (2H, m), 8.22 (1H, d, J=9.3Hz).

MS (FAB) m/z: 468 [(M+H)⁺, Cl³⁵], 470 [(M+H)⁺, Cl³⁷].

[0730]

[Referential Example 83]

3-Ethoxycarbonyl-1-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine

A saturated ethanol hydrochloride solution was added to tert-butyl-1-(3-ethoxycarbonyl)piperazine carboxylate (3.97 g) and the mixture was stirred for 30 minutes. After the solvent was distilled off under reduced pressure, the residue was suspended in dichloromethane (200 ml). To the resulting suspension, 1-benzenesulfonyl-5-chloroindole-2-sulfonyl chloride (6.00 g) and triethylamine (6.40 ml) were added, followed by stirring at room temperature for 3 hours. Water and dichloromethane were added to the reaction mixture. The organic layer so separated was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the

solvent. The residue was purified by chromatography on a silica gel column (methanol : dichloromethane = 1:20), whereby the title compound (4.44 g, 56%) was obtained as colorless crystals.

[0731]

¹H-NMR (CDCl₃) δ: 1.24 (3H, t, J=6.8Hz), 2.87-2.95 (1H, m), 3.11-3.28 (3H, m), 3.57-3.66 (2H, m), 3.91-3.98 (1H, m), 4.17 (2H, q, J=6.8Hz), 7.38-7.48 (4H, m), 7.55-7.59 (2H, m), 8.03 (2H, d, J=7.8Hz), 8.21 (1H, d, J=9.3Hz).

MS (EI) m/z: 511 (M⁺, Cl³⁵), 513 (M⁺, Cl³⁷)+.

[0732]

[Referential Example 84]

1-tert-Butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

To 1-tert-butoxycarbonyl-4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine (4.84 g), a 0.5N methanol solution of sodium hydroxide (20 ml) was added, followed by stirring at room temperature for 1 hour. Under ice cooling, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. Water and dichloromethane were then added and the organic layer was collected. The organic layer was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (methanol : dichloromethane = 1:20), whereby the title compound (3.33 g, 93%) was obtained as colorless powder.

[0733]

¹H-NMR (CDCl₃) δ: 1.40 (9H, s), 3.05-3.14 (4H, m), 3.48-3.57 (4H, m), 6.96 (1H, d, J=2.0Hz), 7.33 (1H, dd, J=8.8, 2.0Hz), 7.38 (1H, d, J=8.8Hz), 7.67 (1H, d, J=2.0Hz), 8.78 (1H, br).
MS (FAB) m/z: 400 [(M+H)⁺, Cl³⁵], 402 [(M+H)⁺, Cl³⁷].

[0734]

In the same manner as in Referential Example 84, the compound shown in Referential Example 85 was synthesized.

[0735]

[Referential Example 85]

1-[(5-Chloroindol-2-yl)sulfonyl]-3-methoxycarbonylpiperazine

[0736]

¹H-NMR (CDCl₃) δ: 2.70-2.82 (1H, m), 2.84-2.97 (2H, m), 3.06-3.16 (1H, m), 3.37-3.46 (1H, m), 3.61 (1H, dd, J=8.3, 3.4Hz), 3.69-3.80 (1H, m), 3.75 (3H, s), 6.98 (1H, s), 7.32 (1H, dd, J=8.8, 2.0Hz), 7.38 (1H, d, J=8.8Hz), 7.67 (1H, s), 8.80 (1H, s).
MS (EI) m/z: 357 (M⁺, Cl³⁵), 359 (M⁺, Cl³⁷).

[0737]

[Referential Example 86]

3-(N-Methylcarbamoyl)-1-[(5-chloroindol-2-yl)sulfonyl]piperazine

In tetrahydrofuran (25 ml), 1-[(5-chloroindol-2-yl)sulfonyl]-3-methoxycarbonylpiperazine (480 mg) was dissolved. After a 0.2N methanol solution of sodium hydroxide

(7 ml) and water (2 ml) were added to the resulting solution and the mixture was stirred at room temperature for 1 hour, the solvent was distilled off under reduced pressure. The resulting yellow amorphous substance (520 mg) was dissolved in N,N-dimethylformamide (60 ml). At room temperature, 1-hydroxybenzotriazole (18.1 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (334 mg), methylamine hydrochloride (90.5 mg) and N-methylmorpholine (271 mg) were added to the resulting solution, followed by stirring at room temperature for 12 hours. The solvent was then distilled off under reduced pressure. Water and ethyl acetate were added to the residue and the organic layer was collected. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol: dichloromethane = 1:50), whereby the title compound (140 mg, 29%) was obtained as a brown amorphous solid.

[0738]

¹H-NMR (DMSO-d₆) δ: 2.39-2.52 (2H,m), 2.64 (3H,d,J=3.9Hz), 2.18-2.30 (1H,m), 2.94-3.00 (1H,m), 3.20-3.37 (2H,m), 3.57-3.66 (1H,m), 6.90-6.95 (1H,br), 7.22-7.27 (1H,br), 7.44-7.49 (1H,m), 7.66-7.78 (2H,m), 8.04-8.17 (3H,m), 12.24 (1H,m).

[0739]

[Referential Example 87]

1-[(5-Chloroindol-2-yl)sulfonyl]piperazine

In methanol (100 ml), 1-tert-butoxycarbonyl-4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine (3.63 g) was dissolved. Under ice cooling, a 0.2N methanol solution of sodium hydroxide (100 ml) was added to the resulting solution, followed by stirring at room temperature for 12 hours. After a saturated aqueous solution of ammonium chloride was added to the reaction mixture under ice cooling, water and dichloromethane were added and the organic layer was collected. The organic layer was dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure. After the solid so precipitated was collected by filtration, it was dissolved in saturated ethanol hydrochloride, followed by stirring for 30 minutes. The reaction mixture was distilled under reduced pressure to remove the solvent, followed by drying under reduced pressure, whereby the title compound (1.25 g, 54%) was obtained as colorless powder.

[0740]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.25-3.43 (8H, br), 7.46 (1H, d, $J=8.8\text{Hz}$), 7.64 (1H, d, $J=8.8\text{Hz}$), 7.93 (1H, s), 9.33 (1H, br), 12.70 (1H, br).

MS (EI) m/z : 298 (M^+ , Cl^{35}), 300 (M^+ , Cl^{37}).

Elementary analysis for $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{O}_2\text{S}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 41.75; H, 4.67; Cl, 20.54; N, 12.17; S, 9.29.

Found: C, 41.78; H, 4.98; Cl, 20.40; N, 11.88; S, 9.34.

[0741]

[Referential Example 88]

1-tert-Butoxycarbonyl-4-[(5-chloro-1-methylindol-2-yl)sulfonyl]piperazine

Sodium hydride (about 60% in oil, 50.3 mg) washed twice with petroleum ether was suspended in tetrahydrofuran (10 ml), followed by the addition of a solution of 1-tert-butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (457 mg) in tetrahydrofuran (10 ml) under ice cooling. The resulting mixture was stirred for 30 minutes. Under ice cooling, iodomethane (179 mg) was added to the reaction mixture. The resulting mixture was heated to room temperature and stirred for 85 hours. Water and diethyl ether were added and the organic layer was collected. The organic layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol: dichloromethane = 1:50), whereby the title compound (270 mg, 57%) was obtained as colorless powder.

[0742]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (9H, s), 3.14-3.21 (4H, m), 3.48-3.55 (4H, m), 3.96 (3H, s), 7.06 (1H, s), 7.31 (1H, d, $J=9.3\text{Hz}$), 7.36 (1H, d, $J=9.3, 2.0\text{Hz}$), 7.66 (1H, d, $J=2.0\text{Hz}$).
 MS (FAB) m/z : 413 [$(\text{M}+\text{H})^+$, Cl^{35}], 415 [$(\text{M}+\text{H})^+$, Cl^{37}].

[0743]

In the same manner as in Referential Example 88, the compound shown in Referential Example 89 was synthesized.

[0744]

[Referential Example 89]

1-tert-Butoxycarbonyl-4-[(5-chloro-1-ethoxycarbonylmethylindol-2-yl)sulfonyl]piperazine

[0745]

¹H-NMR (CDCl₃) δ: 1.27(3H,t,J=7.3Hz), 1.43(9H,s), 3.10-3.19(4H,m), 3.45-3.53(4H,m), 4.22(2H,q,J=7.3Hz), 5.15(2H,s), 7.15(1H,s), 7.17(1H,d,J=8.8Hz), 7.26(1H,s), 7.36(1H,dd,J=8.8,2.0Hz), 7.68(1H,d,J=2.0Hz).

MS (FAB) m/z: 485 [(M+H)⁺, Cl³⁵], 487 [(M+H)⁺, Cl³⁷].

[0746]

[Referential Example 90]

6-Chloro-2-mercaptobenzothiazole

Under ice cooling, a solution of p-chloroaniline (5.70 g) in acetic acid (7 ml) was added dropwise to disulfur dichloride (25.0 ml) over 30 minutes, followed by stirring at room temperature for 3 hours and then at about 80°C for 3 hours. Benzene (50 ml) was added to the reaction mixture. The green crystals were collected by filtration and washed with benzene. The resulting crystals were dissolved in ice water (500 ml) and the solution was stirred for 1 hour. To the reaction mixture, a 6N aqueous solution of sodium hydroxide was added to make the mixture alkaline. Sodium bicarbonate (6 g) was then added and the mixture was stirred at 100°C for 1 hour. Activated carbon

was added to the reaction mixture, followed by Celite filtration. To the filtrate, carbon disulfide (2.70 ml) was added, followed by heating to about 50°C. Stirring was then conducted for 1.5 hours. After cooling to room temperature, the reaction mixture was made acidic with 1N hydrochloric acid. Colorless powder thus precipitated was collected by filtration and dried, whereby the title compound (1.30 g, 14%) was obtained.

[0747]

¹H-NMR (DMSO-d₆) δ: 7.28 (1H, d, J=8.3Hz),

7.45 (1H, dd, J=8.3, 2.0Hz), 7.86 (1H, d, J=2.0Hz).

MS (FAB) m/z: 202 [(M+H)⁺, Cl³⁵], 204 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₇H₄ClNS₂

Calculated: C, 41.68; H, 2.00; Cl, 17.58; N, 6.94; S, 31.80.

Found: C, 41.64; H, 2.13; Cl, 17.83; N, 6.94; S, 31.70.

[0748]

[Referential Example 91]

1-tert-Butoxycarbonyl-4-[(5-chloroenzothiazol-2-yl)sulphenyl]piperazine

At room temperature, tert-butyl-1-piperazine carboxylate (5.58 g), 5-chloro-2-mercaptobenzothiazole (1.21 g) and sodium hydroxide (0.48 g) were dissolved in water (25 ml), followed by the dropwise addition of an aqueous solution (25 ml) containing iodine (1.53 g) and potassium iodide (1.65 g). The colorless crystals so precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby the title compound (1.1 g, 48%) was obtained.

[0749]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 3.24 (4H, br), 3.58 (4H, br s), 7.26 (1H, m), 7.70 (1H, d, $J=8.3\text{Hz}$), 7.81 (1H, s).
MS (FAB) m/z : 386 [$(\text{M}+\text{H})^+$, Cl^{35}], 388 [$(\text{M}+\text{H})^+$, Cl^{37}].

[0750]

In the same manner as in Referential Example 91, the compound shown in Referential Example 92 was synthesized.

[0751]

[Referential Example 92]

1-tert-Butoxycarbonyl-4-[(6-chlorobenzothiazol-2-yl)sulphenyl]piperazine

[0752]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 3.24 (4H, br s), 3.58 (4H, br s), 7.37 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.73 (1H, d, $J=8.8\text{Hz}$), 7.77 (1H, d, $J=2.0\text{Hz}$).
MS (FAB) m/z : 386 [$(\text{M}+\text{H})^+$, Cl^{35}], 388 [$(\text{M}+\text{H})^+$, Cl^{37}].

[0753]

[Referential Example 93]

1-tert-Butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulfonyl]piperazine

At room temperature, 1-tert-butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulphenyl]piperazine (1.10 g) and potassium carbonate (1.30 g) were suspended in a mixed solvent of ethanol (30 ml) and water (10 ml), followed by the dropwise addition of a solution of 3-chloroperbenzoic acid (2.11 g) in

ethanol (25 ml) at 0°C. The reaction mixture was heated to room temperature and stirred for 24 hours. Sodium thiosulfate and ethyl acetate were added and the organic layer was collected. The organic layer thus obtained was dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent was purified by chromatography on a silica gel column (dichloromethane ~ 2% methanol - dichloromethane), whereby the title compound (293 mg, 25%) was obtained.

[0754]

¹H-NMR (CDCl₃) δ: 1.43 (9H, s), 3.35-3.43 (4H, m), 3.51-3.58 (4H, m), 7.55 (1H, dd, J=8.8, 1.5 Hz), 7.90 (1H, d, J=8.8 Hz), 8.18 (1H, d, J=1.5 Hz).

MS (FAB) m/z: 418 [(M+H)⁺, Cl³⁵], 420 [(M+H)⁺, Cl³⁷].

[0755]

In the same manner as in Referential Example 93, the compound shown in Referential Example 94 was synthesized.

[0756]

[Referential Example 94]

1-tert-Butoxycarbonyl-4-[(6-chlorobenzothiazol-2-yl)sulfonyl]piperazine

[0757]

¹H-NMR (CDCl₃) δ: 1.43 (9H, s), 3.35-3.43 (4H, m), 3.50-3.58 (4H, m), 7.59 (1H, dd, J=8.8, 2.0 Hz), 7.97 (1H, d, J=2.0 Hz), 8.10 (1H, d, J=8.8 Hz).

MS (FAB) m/z: 418 [(M+H)⁺, Cl³⁵], 420 [(M+H)⁺, Cl³⁷].

[0758]

[Referential Example 95]

1-[(5-Chlorobenzothiazol-2-yl)sulfonyl]piperazine
hydrochloride

At room temperature, 1-tert-butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulfonyl]piperazine (293 mg) was suspended in dichloromethane (100 ml), followed by the addition of saturated ethanol hydrochloride (10 ml). The resulting mixture was stirred for 30 minutes. The solvent was then distilled off under reduced pressure. Ethyl acetate was added and the resulting colorless powder was collected by filtration, whereby the title compound (165 mg, 66%) was obtained.

[0759]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.23(4H, br s), 3.56(4H, br s),
7.78(1H, dd, $J=8.8, 2.0\text{Hz}$), 8.39-8.43(2H, m).

MS (FAB) m/z : 318 [(M+H) $^+$, Cl 35], 320 [(M+H) $^+$, Cl 37].

[0760]

In the same manner as in Referential Example 95, the compounds shown in Referential Examples 96 to 100 were synthesized.

[0761]

[Referential Example 96]

1-[(6-Chlorobenzothiazol-2-yl)sulfonyl]piperazine
hydrochloride

[0762]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.21-3.27(4H,m), 3.52-3.57(4H,m),
7.79(1H,dd,J=8.8,2.0Hz), 8.28(1H,d,J=8.8Hz),
8.53(1H,d,J=2.0Hz).

MS (FAB) m/z : 318 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 320 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{11}\text{H}_{12}\text{ClN}_3\text{O}_2\text{S}_2 \cdot 1.05\text{HCl} \cdot 0.5\text{H}_2\text{O}$
Calculated: C, 36.19; H, 3.88; Cl, 19.91; N, 11.51;
S, 17.57.

Found: C, 36.19; H, 4.10; Cl, 20.08; N, 11.50;
S, 17.19.

[0763]

[Referential Example 97]

1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazine

[0764]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.20(4H,br), 3.45(4H,br),
7.62(1H,d,J=8.8Hz), 7.76(1H,s), 7.85(1H,d,J=8.8Hz),
7.96(1H,s), 9.41(1H,br).

MS (FAB) m/z : 301 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 303 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S} \cdot \text{HCl} \cdot 0.1\text{H}_2\text{O}$
Calculated: C, 42.51; H, 4.22; Cl, 20.91; N, 8.26; S, 9.46.
Found: C, 42.38; H, 4.33; Cl, 20.92; N, 8.18; S, 9.58.

[0765]

[Referential Example 98]

1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazine

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.20(4H,t,J=4.9Hz), 3.42(4H,t,J=4.9Hz),
7.51(1H,d,J=7.8Hz), 7.82(1H,s), 7.89(1H,d,J=7.8Hz),

9.18 (1H, br) .

MS (FAB) m/z: 301 [(M+H)⁺, Cl³⁵], 303 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₁₂H₁₃ClN₂O₃S·HCl·0.5H₂O

Calculated: C, 41.63; H, 4.37; Cl, 20.48; N, 8.09; S, 9.26.

Found: C, 41.54; H, 4.32; Cl, 20.49; N, 7.90; S, 9.07.

[0766]

[Referential Example 99]

1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

[0767]

¹H-NMR (DMSO-d₆) δ: 3.20-3.50 (8H, m), 7.64 (1H, dd, J=8.8, 2.0 Hz),

8.12 (1H, s), 8.20 (1H, s), 8.23 (1H, d, J=8.8 Hz), 9.22 (2H, br s).

MS (FAB) m/z: 317 [(M+H)⁺, Cl³⁵], 319 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₁₂H₁₃ClN₂O₂S₂·HCl·1.6H₂O

Calculated: C, 37.72; H, 4.54; Cl, 18.56; N, 7.33; S, 16.78.

Found: C, 37.56; H, 4.67; Cl, 18.72; N, 7.17; S, 16.56.

[0768]

[Referential Example 100]

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

[0769]

¹H-NMR (DMSO-d₆) δ: 3.20-3.38 (8H, m), 7.59 (1H, dd, J=8.8, 2.0 Hz),

8.10 (1H, d, J=8.8 Hz), 8.16 (1H, s), 8.36 (1H, d, J=8.8 Hz),

9.29 (2H, br s).

MS (FAB) m/z: 317 [(M+H)⁺, Cl³⁵], 319 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₁₂H₁₃ClN₂O₂S₂·HCl

Calculated: C, 40.80; H, 3.99; Cl, 20.07; N, 7.93;

S, 18.15.

Found: C, 40.64; H, 4.04; Cl, 20.06; N, 7.90;

S, 17.91.

[0770]

[Referential Example 101]

1-tert-Butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine

In methanol (1000 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[ethoxycarbonyl]piperazine hydrochloride (WO96/10022) (43.0 g) was dissolved, followed by the addition of triethylamine (17.1 ml) and di-tert-butyl dicarbonate (27.0 g). The resulting mixture was stirred at room temperature for 3 hours. The residue obtained by concentration of the reaction mixture under reduced pressure was added with ethyl acetate and the resulting mixture was washed with 1N hydrochloric acid. The organic layer thus extracted was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 8:1), whereby the title compound (46.0 g, 93%) was obtained as a colorless solid.

[0771]

¹H-NMR (CDCl₃) δ: 1.24-1.32 (3H, m), 1.33-1.50 (9H, m), 2.37 (1H, m), 2.54 (1H, d, J=10.7Hz), 3.15-3.41 (1H, m), 3.68-4.08 (2H, m), 4.10-4.39 (3H, m), 4.62 (1/2H, br s), 4.82 (1/2H, br s), 7.58 (1H, dd, J=8.8, 2.0Hz), 7.75 (1H, dd, J=8.8, 2.0Hz), 7.87-7.94 (3H, m), 8.31 (1H, d, J=2.0Hz).

MS (FAB) m/z : 483 $[(M+H)^+, Cl^{35}]$, 485 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{22}H_{27}ClNO_6S$

Calculated: C, 54.71; H, 5.63; Cl, 7.34; N, 5.80; S, 6.64.

Found: C, 54.89; H, 5.42; Cl, 7.15; N, 5.76; S, 6.24.

[0772]

[Referential Example 102]

1-tert-Butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid

In tetrahydrofuran (40 ml), 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine (23.0 g) was dissolved, followed by the addition of ethanol (40 ml) and a 3N aqueous sodium hydroxide solution (30 ml). The resulting mixture was stirred at room temperature for 3 hours. To the reaction mixture, 1N hydrochloric acid was added to make it acidic and then ethyl acetate was added and the organic layer was collected. The organic layer was dried over anhydrous sodium sulfate. The solid precipitated by distilling off the solvent under reduced pressure was collected by filtration, whereby the title compound (23.8 g, quant.) was obtained as a colorless solid.

[0773]

1H -NMR ($CDCl_3$) δ : 2.41 (1H, m), 2.59 (1H, m), 3.15-3.38 (1H, m), 3.70-4.08 (2H, m), 4.20-4.39 (1H, m), 4.72 (1/2H, br s), 4.91 (1/2H, br s), 7.58 (1H, dd, $J=8.8$, $J=2.0$ Hz), 7.76 (1H, dd, $J=8.8$, $J=2.0$ Hz), 7.87-7.95 (3H, m), 8.34 (1H, s).

Mass (FAB) m/z : 455((M+H)⁺, Cl³⁵], 457((M+H)⁺, Cl³⁷].

Elementary analysis for C₂₀H₂₃ClNO₆S

Calculated: C, 52.80; H, 5.10; Cl, 7.79; N, 6.16; S, 7.05.

Found: C, 52.62; H, 5.00; Cl, 7.75; N, 6.22; S, 6.83.

[0774]

[Referential Example 103]

1-tert-Butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 101 or 102, the title compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[methoxycarbonylmethyl]piperazine as a raw material.

[0775]

¹H-NMR (DMSO-d₆) δ: 1.38 (9H, s), 2.32 (1H, dt, J=12.2, 3.4Hz), 2.48 (1H, dd, J=12.2, 3.4Hz), 2.61 (1H, dd, J=15.6, 5.9Hz), 2.86 (1H, dd, J=15.6, 8.3Hz), 3.13 (1H, s), 3.68 (3H, s), 3.74-4.08 (3H, m), 7.58 (1H, dd, J=8.8, 2.0Hz), 7.74 (1H, dd, J=8.8, 2.0Hz), 7.89-7.94 (3H, m), 8.29 (1H, s).

MS (FAB) m/z : 469 [(M+H)⁺, Cl³⁵], 471 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₇ClN₂O₇S

Calculated: C, 54.71; H, 5.63; Cl, 7.34; N, 5.80; S, 6.64.

Found: C, 54.74; H, 5.69; Cl, 7.34; N, 5.84; S, 6.62.

[0776]

Referential Example 104

6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

In anhydrous tetrahydrofuran (500 ml), 6-ethoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (WO94/21599) (21.0 g) was dissolved, followed by the addition of a solution of lithium aluminum hydride in tetrahydrofuran (a 1.0M solution, 200 ml) under ice cooling. The resulting mixture was stirred at room temperature for 2 hours. Water (7 ml) was then added to the reaction mixture in portions. After the termination of the reaction, a 1N aqueous potassium hydroxide solution (7 ml) and anhydrous magnesium sulfate were successively added. After removal of the insoluble matter by filtration, the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by distillation under reduced pressure (1.5 mmHg, boiling point: 82 to 85°C), whereby the title compound (6.10 g, 40%) was obtained as a colorless oil.

[0777]

¹H-NMR (CDCl₃) δ: 2.52 (3H, s), 2.83 (2H, t, J=5.9Hz), 2.98 (2H, t, J=5.9Hz), 3.70 (2H, s), 3.87 (2H, br s), 8.63 (1H, s).
MS (FAB) m/z: 155 [(M+H)⁺].

[0778]

[Referential Example 105]

Lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate

In anhydrous tetrahydrofuran (200 ml), 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (6.43 g) was dissolved, followed by the dropwise addition of a solution

(1.47M, 34.00 ml) of n-butyl lithium in n-hexane at an external temperature of -78°C. The resulting mixture was stirred for 40 minutes without changing the temperature. Then a carbon dioxide gas was blown into the reaction mixture for 1 hour. After heating to room temperature, the reaction mixture was concentrated under reduced pressure, whereby the title compound (9.42 g, quant.) was obtained as a pale brown foamy solid.

[0779]

¹H-NMR (DMSO-d₆) δ: 2.37(3H,s), 2.64-2.77(4H,m), 3.54(2H,s).

MS (FAB) m/z: 199 (M+H)⁺.

[0780]

[Referential Example 106]

N-[[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]glycine ethyl ester trifluoroacetate

In the same manner as in Referential Example 6, an amide bond was formed using 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid as a raw material, followed by deprotection using trifluoroacetic acid, whereby the title compound was obtained.

[0781]

¹H-NMR (DMSO-d₆) δ: 1.20(3H,t,J=7.3Hz), 2.47-2.82(2H,m),

3.14-3.28(1H,m), 3.30-3.39(1H,m), 3.72-3.79(1H,m),

3.95(2H,d,J=5.9Hz), 4.08-4.18(3H,m),

4.20(1H,dd,J=11.2,3.4Hz), 7.75(1H,dd,J=8.8,2.0Hz),

7.84(1H,d,J=8.8Hz), 8.23(1H,d,J=8.8Hz), 8.28(1H,s),

8.30 (1H, d, J=8.8Hz), 8.55 (1H, s), 9.29 (1H, t, J=5.9Hz).

MS (FAB) m/z: 440 [(M+H)⁺, Cl³⁵], 442 [(M+H)⁺, Cl³⁷].

[0782]

[Referential Example 107]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(morpholin-4-yl)carbonyl]methyl]piperazine hydrochloride

In the same manner as in Referential Example 6, an amide bond was formed using 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine and morpholine as raw materials, followed by deprotection In the same manner as in Referential Example 1, whereby the title compound was obtained.

[0783]

¹H-NMR (DMSO-d₆) δ: 2.65-2.91 (4H, m), 3.10-3.22 (1H, m), 3.30-3.82 (12H, m), 7.74 (1H, d, J=8.8Hz), 7.84 (1H, d, J=8.8Hz), 8.20 (1H, d, J=8.8Hz), 8.22-8.31 (2H, m), 8.55 (1H, s), 9.18 (1H, br s), 9.32 (1H, br s).

MS (FAB) m/z: 438 [(M+H)⁺, Cl³⁵], 440 [(M+H)⁺, Cl³⁷].

[0784]

[Referential Example 108]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[N-(morpholin-4-yl)carbamoyl]piperazine trifluoroacetate

In the same manner as in Referential Example 106, the title compound was obtained.

[0785]

$^1\text{H-NMR}$ (DMSO-d_6 at 100°C) δ : 2.59-3.97 (13H, m), 4.00-4.12 (1H, m), 4.38-4.50 (1H, m), 7.68 (1H, dd, $J=8.8, 2.4\text{Hz}$), 7.84 (1H, d, $J=8.8\text{Hz}$), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.18 (1H, s), 8.22 (1H, d, $J=8.8\text{Hz}$), 8.48 (1H, s), 9.18 (1H, br s).

MS (FAB) m/z : 439 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 441 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0786]

[Referential Example 109]

Ethyl N' -[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]hydrazinoacetate hydrochloride

In the same manner as in Referential Example 106, the title compound was obtained.

[0787]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.20-1.24 (3H, m), 2.55-2.90 (2H, m), 3.00-3.20 (1H, m), 3.30-3.38 (1H, m), 3.53-3.87 (3H, m), 3.94-4.19 (3H, m), 4.27 (1/2H, d, $J=9.8\text{Hz}$), 4.54-4.63 (1/2H, m), 4.95 (1H, br s), 7.75 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.84-7.95 (1H, m), 8.19-8.32 (3H, m), 8.56 (1H, s), 8.80-9.00 (1H, m), 9.78-10.20 (1H, m).

MS (FAB) m/z : 455 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 457 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0788]

[Referential Example 110]

4-(Aminoacetyl)morpholiné hydrochloride

In N,N -dimethylformamide (100 ml), N -tert-butoxycarbonylglycine (2.00 g), morpholine (1.00 ml), 1-hydroxybenzotriazole monohydrate (1.74 g) and 1-

(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.84 g) were dissolved, followed by stirring overnight at room temperature. After concentration under reduced pressure, the residue was diluted with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 100:1), whereby a colorless foam was obtained. The substance was dissolved in dichloromethane (2 ml), followed by the addition of saturated ethanol hydrochloride (10 ml). The resulting mixture was stirred at room temperature for 5 minutes. The reaction mixture was concentrated to dryness under reduced pressure, whereby the title compound (1.80 g, quant.) was obtained as a pale yellow foam.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.39 (2H, t, $J=4.5\text{Hz}$), 3.48 (2H, t, $J=4.5\text{Hz}$), 3.52-3.63 (4H, m), 3.77-3.90 (2H, m), 8.32 (3H, br s).

MS (FAB) m/z : 145 ($M+H$) $^+$.

[0789]

[Referential Example 111]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[N-[(morpholin-4-yl)carbonyl]methyl]carbamoylpiperazine hydrochloride

In the same manner as in Referential Example 106, the title compound was obtained.

[0790]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.67 (1H, d, $J=11.2\text{Hz}$), 2.79 (1H, d, $J=11.2\text{Hz}$),

3.09-3.18 (1H, m), 3.17-3.30 (1H, m), 3.42 (1H, d, J=13.2Hz),
 3.45-3.74 (8H, m), 3.82 (1H, d, J=12.2Hz), 4.10-4.30 (4H, m),
 7.86 (1H, d, J=8.8Hz), 7.95 (1H, d, J=8.8Hz), 8.32 (1H, d, J=8.8Hz),
 8.40 (1H, s), 8.41 (1H, d, J=8.8Hz), 8.67 (1H, d, J=8.8Hz),
 8.93 (1H, br s), 9.12 (1H, d, J=4.9Hz), 10.03 (1H, br s).

MS (FAB) m/z: 481 [(M+H)⁺, Cl³⁵], 483 [(M+H)⁺, Cl³⁷].

[0791]

[Referential Example 112]

1-Benzyl-4-tert-butoxycarbonylpiperazine

In acetonitrile (80 ml), tert-butyl-1-piperazine
 carboxylate (2.50 g) was dissolved. Under ice cooling, benzyl
 bromide (1.59 ml) and triethylamine (1.87 ml) were added
 dropwise to the resulting solution, followed by stirring at room
 temperature for 90 minutes. After the solvent was distilled
 off under reduced pressure, distilled water and dichloromethane
 were added to the residue and the organic layer was collected.
 The organic layer was washed with saturated saline and dried
 over anhydrous sodium sulfate. The residue obtained by
 distilling off the solvent under reduced pressure was purified
 by chromatography on a silica gel column (ethyl acetate : hexane
 = 1:20 to 1:5), whereby the title compound (3.12 g, 84%) was
 obtained as colorless powder.

[0792]

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, J=4.9Hz),
 3.42 (4H, t, J=4.8Hz), 3.51 (2H, s), 7.25-7.29 (1H, m), 7.30-
 7.33 (4H, m).

MS (EI) m/z: 276M⁺.

[0793]

[Referential Example 113]

1-Benzylpiperazine

To 1-benzyl-4-tert-butoxycarbonylpiperazine (3.12 g), saturated ethanol hydrochloride was added, followed by stirring for 90 minutes at room temperature. The solvent was distilled off under reduced pressure, followed by drying, whereby the title compound (2.73 g, 97%) was obtained as white powder.

[0794]

¹H-NMR (DMSO-d₆) δ: 3.05-3.67 (9H, m), 4.38 (2H, br), 7.35-7.70 (5H, m), 9.61 (1H, br).

MS (EI) m/z: 176M⁺.

Elementary analysis for C₁₁H₁₆N₂·2HCl·0.2H₂O

Calculated: C, 52.27; H, 7.34; Cl, 28.05; N, 11.27.

Found: C, 52.04; H, 7.36; Cl, 27.89; N, 11.24.

[0795]

[Referential Example 114]

1-Benzyl-4-sulfamoylpiperazine

Chlorosulfonyl isocyanate (0.35 ml) was dissolved in dichloromethane (5 ml). Under ice cooling, tert-butanol (0.21 ml) was added dropwise to the resulting solution, followed by stirring for 30 minutes. After the reaction mixture was added dropwise to a solution of 1-benzylpiperazine dihydrochloride (0.25 g) in dichloromethane (20 ml) under ice cooling,

triethylamine (0.28 ml) was added. The mixture was stirred for 30 minutes under ice cooling and then at room temperature for 1 hour. Distilled water and dichloromethane were added and the organic layer was collected. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol : dichloromethane = 1:50 to 1:25), whereby 1-benzyl-[4-(N-tert-butoxycarbonyl)sulfamoyl]piperazine was obtained as colorless powder. To the resulting powder, saturated ethanol hydrochloride was added and the mixture was stirred at room temperature for 1 hour. After the solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium bicarbonate and dichloromethane were added to the residue and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (0.26 g, quant.) was obtained as colorless powder.

[0796]

$^1\text{H-NMR}$ (CDCl_3) δ : 2.58 (4H, t, $J=4.9\text{Hz}$), 3.22 (4H, t, $J=4.9\text{Hz}$), 3.56 (2H, s), 4.33 (2H, br), 7.27-7.36 (5H, m).

MS (EI) m/z : 255 M^+ .

[0797]

[Referential Example 115]

3,4-Bis(bromomethyl)-1-chlorobenzene

In acetonitrile (500 ml), 1-chloro-3,4-dimethylbenzene (20.0 ml) was dissolved and to the resulting solution, N-bromosuccinimide (53.0 g) and azoisobutyronitrile (1.20 g) were added, followed by heating under reflux for 1 hour. After cooling, the solvent was distilled off under reduced pressure and dichloromethane was then added to the residue. From the resulting mixture, the precipitate was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane), whereby the title compound (41.5 g, 93%) was obtained as a colorless oil.

[0798]

¹H-NMR (CDCl₃) δ: 4.59 (2H, s), 4.61 (2H, s), 7.27-7.36 (3H, m).

MS (EI) m/z: 295M⁺.

[0799]

[Referential Example 116]

1-Benzyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

In ethanol (5 ml), 1-benzyl-4-sulfamoylpiperazine (251 mg) was dissolved. To the resulting solution, 3,4-bis(bromomethyl)-1-chlorobenzene (293 mg) and potassium carbonate (204 mg) were added, followed by heating under reflux for 3.5 hours. After cooling, the precipitate was filtered off. The filtrate was then distilled under reduced pressure and the residue was purified by chromatography on a silica gel column (dichloromethane ~ ethanol : dichloromethane = 1:100), whereby

the title compound (222 mg, 58%) was obtained.

[0800]

$^1\text{H-NMR}$ (CDCl_3) δ : 2.37-2.58 (4H, m), 3.24-3.41 (4H, m), 3.53 (2H, s), 4.64 (4H, m), 7.13-7.34 (8H, m).

MS (FAB) m/z : 392 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 394 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0801]

[Referential Example 117]

1-[(5-Chloroisoindol-2-yl)sulfonyl]piperazine

To a solution of 1-benzyl-4-[(5-chloroisoindol-2-yl)sulfonyl]piperazine (222 mg) in 1,2-dichloroethane (20 ml), 1-chloroethyl chloroformate (81 mg) was added under ice cooling. The resulting mixture was stirred for 15 minutes and then heated under reflux for 1 hour. After cooling, anhydrous methanol was added to the residue obtained by distilling off the solvent under reduced pressure. The mixture was heated under reflux for 11 hours. After cooling, the residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (ethanol : dichloromethane = 1:50 to 1:10), whereby the title compound (120 mg, 70%) was obtained.

[0802]

$^1\text{H-NMR}$ (CDCl_3) δ : 2.96 (4H, t, $J=4.4\text{Hz}$), 3.09-3.22 (1H, br), 3.30 (4H, t, $J=4.4\text{Hz}$), 4.65 (4H, m), 7.14-7.35 (3H, m).

MS (FAB) m/z : 302 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 304 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0803]

[Referential Example 118]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine trifluoroacetate

In the same manner as in Referential Example 6, 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid was reacted with methylamine to form an amide bond and then the protecting group was removed using trifluoroacetic acid, whereby the title compound was obtained.

¹H-NMR (DMSO-d₆) δ: 2.54-2.65 (2H, m), 2.67 (3H, d, J=3.9Hz), 3.12-3.22 (1H, m), 3.33 (1H, d, J=13.2Hz), 3.70 (1H, d, J=12.2Hz), 4.04 (2H, d, J=8.8Hz), 7.75 (1H, dd, J=8.8, 2.0Hz), 7.87 (1H, d, J=8.8Hz), 8.20 (1H, d, J=8.8Hz), 8.27 (1H, s), 8.29 (1H, d, J=8.8Hz), 8.58 (1H, s), 8.70 (1H, d, J=4.4Hz), 9.06 (1H, br s).

MS (FAB) m/z: 440 [(M+H)⁺, Cl³⁵], 442 [(M+H)⁺, Cl³⁷].

[0804]

In the same manner as in Referential Example 118, Compounds of Referential Examples 119 to 124 were synthesized.

[0805]

[Referential Example 119]

4-[[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]morpholine trifluoroacetate

[0806]

¹H-NMR (DMSO-d₆) δ: 2.49-2.58 (1H, m), 2.64-2.75 (1H, m), 3.09-

3.81 (1H, m), 3.93 (1H, d, J=12.2Hz), 4.76 (1H, dd, J=10.7, 2.4Hz),
7.75 (1H, d, J=8.8Hz), 7.90 (1H, d, J=8.8Hz), 8.21 (1H, d, J=8.8Hz),
8.27 (1H, s), 8.29 (1H, d, J=8.8Hz), 8.58 (1H, s), 9.15 (1H, br s).

MS (FAB) m/z: 440 [(M+H)⁺, Cl³⁵], 442 [(M+H)⁺, Cl³⁷].

[0807]

[Referential Example 120]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(N-tert-butoxy)carbonyl]piperazine trifluoroacetate

[0808]

¹H-NMR (DMSO-d₆) δ: 2.58-2.70 (2H, m), 3.14-3.23 (1H, m), 3.30-3.40 (1H, m), 3.64 (1H, d, J=12.2Hz), 3.97 (1H, d, J=12.2Hz),
4.05 (1H, dd, J=10.2, 3.4Hz), 7.74 (1H, dd, J=8.8, 2.0Hz),
7.87 (1H, d, J=8.8Hz), 8.21 (1H, d, J=8.8Hz), 8.27 (1H, d, J=2.0Hz),
8.29 (1H, d, J=8.8Hz), 8.57 (1H, s), 11.24 (1H, s).

MS (FAB) m/z: 426 [(M+H)⁺, Cl³⁵], 428 [(M+H)⁺, Cl³⁷].

[0809]

[Referential Example 121]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(N-isopropyl)carbamoyl]piperazine hydrochloride

[0810]

¹H-NMR (DMSO-d₆) δ: 1.05-1.18 (6H, m), 2.60-2.77 (2H, m), 3.08-3.16 (1H, m), 3.30-3.41 (1H, m), 3.67 (1H, d, J=12.2Hz), 3.80-3.90 (1H, m), 4.99 (2H, d, J=7.8Hz), 7.74 (1H, dd, J=8.8, 2.0Hz),
7.87 (1H, dd, J=8.8, 1.5Hz), 8.22 (1H, d, J=8.8Hz), 8.28 (1H, s),
8.31 (1H, d, J=8.8Hz), 8.58 (1H, s), 8.74 (1H, d, J=7.3Hz).

MS (FAB) m/z : 396 $[(M+H)^+, Cl^{35}]$, 398 $[(M+H)^+, Cl^{37}]$.

[0811]

[Referential Example 122]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[piperazin-1-yl]carbonyl]methyl]piperazine hydrochloride

[0812]

1H -NMR (DMSO- d_6) δ : 1.45-1.90 (8H, m), 2.78 (1H, d, $J=16.1$ Hz), 3.08-3.20 (1H, m), 3.20-3.60 (7H, m), 3.68-3.92 (3H, m), 7.58 (1H, d, $J=8.8$ Hz), 7.71 (1H, d, $J=8.8$ Hz), 7.85-7.98 (3H, m), 8.31 (1H, s), 9.09 (1H, br s), 11.32 (1H, br s).

MS (FAB) m/z : 436 $[(M+H)^+, Cl^{35}]$, 438 $[(M+H)^+, Cl^{37}]$.

[0813]

[Referential Example 123]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[N-(2-methoxybenzyl)]carbonyl]piperazine hydrochloride

[0814]

1H -NMR (DMSO- d_6) δ : 2.69 (1H, t, $J=11.2$ Hz), 2.72-2.30 (1H, m), 3.08-3.16 (1H, m), 3.31-3.37 (1H, m), 3.68 (1H, d, $J=12.2$ Hz), 4.05 (1H, d, $J=12.2$ Hz), 4.14 (1H, dd, $J=10.3, 3.4$ Hz), 4.29 (1H, d, $J=5.4$ Hz), 6.93 (1H, t, $J=7.3$ Hz), 7.02 (1H, d, $J=7.8$ Hz), 7.24 (1H, d, $J=7.3$ Hz), 7.29 (1H, t, $J=7.8$ Hz), 7.77 (1H, dd, $J=8.8, 2.0$ Hz), 7.88 (1H, d, $J=8.8$ Hz), 8.23 (1H, d, $J=8.8$ Hz), 8.30 (1H, s), 8.32 (1H, d, $J=8.8$ Hz), 8.59 (1H, s), 9.17 (1H, t, $J=5.4$ Hz).

MS (FAB) m/z : 474 $[(M+H)^+, Cl^{35}]$, 476 $[(M+H)^+, Cl^{37}]$.

[0815]

[Referential Example 124]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)]carbamoyl]piperazine

[0816]

¹H-NMR (DMSO-d₆) δ: 2.54-2.75 (2H, m), 3.02-3.51 (7H, m), 3.70 (1H, d, J=12.2Hz), 7.75 (1H, d, J=8.8Hz), 7.87 (1H, d, J=8.8Hz), 8.22 (1H, d, J=8.8Hz), 8.28 (1H, s), 8.31 (1H, d, J=8.8Hz), 8.58 (1H, s), 8.97 (1H, t, J=5.4Hz), 10.01 (1H, br s).
MS (FAB) m/z: 412 [(M+H)⁺, Cl³⁵], 414 [(M+H)⁺, Cl³⁷].

[0817]

[Referential Example 125]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[carbamoylmethyl]piperazine hydrochloride

In N,N-dimethylformamide (20 ml), 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (800 mg) was dissolved, followed by the addition of pyridine (0.85 ml), ammonium bicarbonate (417 mg) and di-tert-butoxy carbonate (1.15 g). The resulting mixture was stirred at room temperature for 7 hours. After concentration of the reaction mixture under reduced pressure, the residue was added with dichloromethane, washed with 1N hydrochloric acid and a saturated aqueous solution of sodium bicarbonate, each once and then the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. After the addition of ethanolic saturated

hydrochloric acid (30 ml) to the residue, the resulting mixture was concentrated under reduced pressure. While washing with ethanol, the solid thus precipitated was removed by filtration. The filtrate was then concentrated under reduced pressure. The residue was crystallized in methanol, whereby the title compound (426 mg) was obtained as a colorless solid.

[0818]

IR(KBr) cm^{-1} : 3185, 2917, 2684, 2607, 1677, 1342, 1299, 1170, 1155, 1135, 755, 692, 578.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.58-2.65(1H,m), 2.72-2.83(1H,m), 3.12-3.21(1H,m), 3.30-3.48(3H,m), 3.55-3.81(1H,m), 7.21(1H,br s), 7.66(1H,br s), 7.73(1H,dd, $J=8.8, 2.0\text{Hz}$), 7.85(1H,d, $J=8.8\text{Hz}$), 8.20(1H,d, $J=8.8\text{Hz}$), 8.26(1H,s), 8.29(1H,d, $J=8.8\text{Hz}$), 8.56(1H,s), 9.02-9.23(2H,m).

MS (FAB) m/z : 368 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 370 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0819]

[Referential Example 126]

1-(3-Furyl)-2-nitroethylene

To a solution of 3-furaldehyde (10.0 g) in ethanol (200 ml), nitromethane (6.37 g) was added at room temperature, followed by the dropwise addition of a 10N-aqueous sodium hydroxide solution (11.0 ml) at 0°C. The resulting mixture was stirred for 1 hour. The reaction mixture was poured into a 15% aqueous solution of hydrochloric acid (500 ml). The precipitate so formed was collected by filtration and dried, whereby the title compound (8.01 g) was obtained as a yellowish

white solid.

[0820]

¹H-NMR (CDCl₃) δ: 6.57 (1H, d, J=2.0Hz), 7.39 (1H, d, J=13.4Hz), 7.52 (1H, br s), 7.83 (1H, br s), 7.94 (1H, d, J=13.4Hz).

[0821]

[Referential Example 127]

2-(t-Butoxycarbonylamino)-1-(3-furyl)ethane

In tetrahydrofuran (170 ml), lithium aluminum hydride (2.20 g) was suspended, followed by the dropwise addition of a solution of 1-(3-furyl)-3-nitroethylene (8.00 g) in tetrahydrofuran (80 ml) at room temperature over 2 hours. The resulting mixture was stirred for 30 minutes. After the reaction mixture was cooled to 0°C, ethyl acetate (50 ml) and then water (10 m) were dropwise added thereto. The mixture was stirred for 30 minutes while gradually heated. The reaction mixture was subjected to Celite filtration by using ethyl acetate. After the filtrate was concentrated, the residue was dissolved in methylene chloride (200 ml). Di-t-butyl dicarbonate (12.6 g) was added to the resulting solution at room temperature and the mixture was stirred for 1 hour. The reaction mixture was concentrated and the residue was purified by chromatography on a silica gel column (400 g of silica gel, hexane : ethyl acetate = 15:1 → 8:1), whereby the title compound (4.30 g) was obtained as a pale yellow transparent oil.

[0822]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.44 (9H, s), 2.61 (2H, t, $J=6.8\text{Hz}$), 3.25-3.37 (2H, m), 4.57 (1H, br s), 6.29 (1H, s), 7.26 (1H, s), 7.37 (1H, s).

[0823]

[Referential Example 128]

6-(*t*-Butoxycarbonyl)-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine

Paraformaldehyde (625 mg) and *p*-toluenesulfonic acid (49.5 mg) were added to a solution of 2-(*t*-butoxycarbonylamino)-1-(3-furyl)ethane (2.20 g) in toluene (300 ml), followed by heating under reflux for 2 hours while dehydrating using a Dean Stark apparatus. After the reaction mixture was allowed to cool down to room temperature, a saturated aqueous solution (200 ml) of sodium bicarbonate and ethyl acetate (200 ml) were added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, washed with saturated saline (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (100 g of silica gel, hexane : ethyl acetate = 15:1 \rightarrow 10:1), whereby the title compound (1.04 g) was obtained as a white solid.

[0824]

IR(KBr) cm^{-1} : 3145, 3005, 2976, 2925, 2862, 1695, 1448, 1419, 1365, 1279, 1228, 1165, 1124, 912, 895, 758.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 2.52 (2H, br s), 3.63 (2H, br s), 4.44 (2H, s), 6.25 (1H, s), 7.29 (1H, s).

MS (FAB) m/z : 224 $[(M+H)^+]$, 168 $[(M+H-\text{isobutene}(56))^+]$.

HRMSM + H for ($C_{12}H_{18}NO_3$)

Calculated: 224.1287

Found: 224.1299

[0825]

[Referential Example 129]

6-Methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine

To 6-(*t*-butoxycarbonyl)-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (1.05 g), a saturated methanol hydrochloride solution (30 ml) was added at room temperature. After stirring for 2 hours, the reaction mixture was concentrated. The residue thus obtained was suspended in methylene chloride (20 ml), followed by the addition of methanol (20 ml), triethylamine (1.31 ml), acetic acid (810 ml), formaldehyde (a 37% aqueous solution, 610 ml) and sodium triacetoxyborohydride (1.51 g) at room temperature. The resulting mixture was stirred for 1 hour. To the reaction mixture, a saturated aqueous solution (100 ml) of sodium bicarbonate and methylene chloride (20 ml) were added to cause separation. The water layer was extracted with methylene chloride (3 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : acetone = 1:1 → 1:2 → methylene chloride : methanol = 10:1), whereby the title compound (434 mg) was obtained as a colorless transparent oil.

[0826]

¹H-NMR (CDCl₃) δ: 2.48 (3H, s), 2.56 (2H, t, J=5.6Hz),
2.67 (2H, t, J=5.6Hz), 3.48 (2H, s), 6.23 (1H, d, J=2.0Hz),
7.25 (1H, s).

[0827]

[Referential Example 130]

3-Aminoacrylaldehyde

To a solution of isoxazole (5.00 g) in methanol (100 ml), Raney nickel ("R-100", produced by Nikko Chemical) (about 1.0 g) was added at room temperature. Under a hydrogen atmosphere (3.05 - 2.65 kg/cm²), the resulting mixture was stirred for 3 hours. The reaction mixture was subjected to Celite filtration and the filtrate was concentrated. The residue thus obtained was reprecipitated in a chloroform - hexane system, whereby the title compound (4.91 g, 69.1 mmol, 95%) was obtained as a yellow solid.

[0828]

¹H-NMR (CDCl₃) δ: 4.60-5.20 (2H, br), 5.45 (1H, dd, J=12.7, 8.3Hz),
7.15 (1H, d, J=12.7Hz), 9.18 (1H, d, J=8.3Hz).

¹H-NMR (CD₃OD) δ: 5.55 (1H, dd, J=12.2, 9.3Hz),
7.59 (1H, d, J=12.2Hz), 8.98 (1H, d, J=9.3Hz).

[0829]

[Referential Example 131]

6-(t-Butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidine

Triethylamine (1.50 ml) and pyridinium acetate (30.0 mg)

were added to 1-benzyl-4-piperidone (3.80 g) and 3-aminoacrylaldehyde (2.10 g), followed by stirring under heat at 120°C. After 22 hours, the reaction mixture was allowed to cool down to room temperature and the brown caramel-like substance thus obtained was dissolved in a 3N aqueous solution of hydrochloric acid. The resulting solution was extracted with chloroform (2 x 50 ml). To the water layer, a saturated aqueous solution (50 ml) of sodium bicarbonate was added, followed by extraction with chloroform (3 x 60 ml). The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was distilled (0.90 mmHg, 145 to 150°C), whereby about 3:2 mixture (1.98 g) of 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthylidine in the form of a pale yellow transparent oil and 1-benzyl-4-piperidone as the raw material was obtained.

[0830]

The mixture was dissolved in acetic acid (25 ml). To the resulting solution, 10% palladium-carbon (500 mg) was added, followed by vigorous stirring at 50 to 60°C under a hydrogen atmosphere (about 1 atm). After the stirring was continued for 2 hours, the reaction mixture was allowed to cool down and filtered. By the concentration of the filtrate, a residue containing 5,6,7,8-tetrahydro-1,6-naphthylidine in the form of a colorless transparent oil was obtained.

[0831]

The residue was dissolved in toluene (20 ml), followed by

the addition of a 40% aqueous solution of sodium hydroxide (30 ml) and di-*t*-butyl dicarbonate (3.20 g, 14.7 mmol) at room temperature. After stirring for 10 minutes, water (30 ml) and toluene (20 ml) were added to the reaction mixture to cause separation. The water layer was extracted with toluene (30 ml). The organic layers were combined, washed with saturated saline (50 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : ethyl acetate = 5:1 → 3:1), whereby the title compound (981 mg) was obtained as a colorless transparent oil.

[0832]

IR(KBr) cm^{-1} : 2974, 1693, 1577, 1454, 1419, 1392, 1365, 1288, 1259, 1241, 1228, 1161, 1119, 1097, 989, 930, 881, 862, 789, 768, 737.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (9H, s), 3.01 (2H, t, $J=5.9\text{Hz}$), 3.76 (2H, t, $J=5.9\text{Hz}$), 4.59 (2H, s), 7.13 (1H, dd, $J=7.8, 4.9\text{Hz}$), 7.41 (1H, d, $J=7.8\text{Hz}$), 8.43 (1H, d, $J=4.9\text{Hz}$).

MS (FAB) m/z : 235 $[(M+H)^+]$, 179 $[(M+H)^+-\text{isobutene}(56)]$.

[0833]

[Referential Example 132]

6-(*t*-Butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidin-1-oxide

To a solution of 6-(*t*-butoxycarbonyl)-5,6,7,8-

tetrahydro-1,6-naphthylidine (1.72 g) in methylene chloride (40 ml), metachloroperbenzoic acid (3.80 g) was added at 0°C and the resulting mixture was stirred. Thirty minutes later, dimethyl sulfide (1.62 ml) was added to the reaction mixture, followed by stirring at room temperature for 30 minutes. To the reaction mixture, a saturated aqueous solution (150 ml) of sodium bicarbonate and methylene chloride (30 ml) were added to cause separation. The water layer was extracted with methylene chloride (3 x 30 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column (100 g of silica gel, methylene chloride : methanol = 20:1 → 10:1), whereby the title compound (1.80 g, 7.19 mmol, 98%) was obtained as a colorless transparent oil.

IR(KBr)cm⁻¹: 2976, 2929, 2860, 1697, 1431, 1365, 1263, 1240, 1167, 1115, 1028, 910, 771.

¹H-NMR (CDCl₃) δ: 1.49(9H,s), 3.05(2H,t,J=5.9Hz), 3.75(2H,t,J=5.9Hz), 4.59(2H,s), 7.04(1H,d,J=8.8Hz), 7.14(1H,dd,J=8.8,5.9Hz), 8.18(1H,d,J=5.9Hz).

[0834]

[Referential Example 133]

6-(t-Butoxycarbonyl)-2-cyano-5,6,7,8-tetrahydro-1,6-naphthylidine

To a solution of 6-(t-butoxycarbonyl)-5,6,7,8-

tetrahydro-1,6-naphthylidin-1-oxide (760 mg) in methylene chloride (15 ml), trimethylsilyl cyanide (610 ml) was added at room temperature and the resulting mixture was stirred for 5 minutes. To the reaction mixture, N,N-dimethylcarbonyl chloride (420 ml) was added, followed by stirring for 41 hours. To the reaction mixture, a saturated aqueous solution (50 ml) of sodium bicarbonate and chloroform (30 ml) were added to cause separation. The water layer was extracted with chloroform (30 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : ethyl acetate = 6:1 \rightarrow 2:1), whereby the title compound (697 mg) was obtained as a white solid. The resulting white solid was recrystallized from a hexane - methylene chloride system, whereby colorless needle-like crystals were obtained.

[0835]

IR(KBr) cm^{-1} : 2978, 2933, 2235, 1693, 1685, 1572, 1477, 1458, 1415, 1365, 1267, 1238, 1169, 1161, 1124, 1097, 935, 839, 768.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (9H, s), 3.05 (2H, t, $J=5.9\text{Hz}$), 3.77 (2H, t, $J=5.9\text{Hz}$), 4.67 (2H, s), 7.54 (2H, s).

MS (FAB) m/z : 260 $[(M+H)^+]$, 204 $[(M+H)^+-\text{isobutene}(56)]$.

Elementary analysis for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2$

Calculated: C, 64.85; H, 6.61; N, 16.20.

Found: C, 64.89; H, 6.60; N, 16.57.

[0836]

[Referential Example 134]

6-(t-Butoxycarbonyl)-2-methoxycarbonyl-5,6,7,8-tetrahydro-1,6-naphthylidine

To a solution of 6-(t-butoxycarbonyl)-2-cyano-5,6,7,8-tetrahydro-1,6-naphthylidine (1.25 g) in methanol (40 ml), concentrated hydrochloric acid (40 ml) was added at room temperature and the resulting mixture was stirred at 100°C for 3 hours. After the reaction mixture was allowed to cool down to room temperature, it was gradually poured into tetrahydrofuran (150 ml) and an aqueous solution (250 ml) of sodium carbonate (40 g), which had been stirred in advance, followed by the addition of di-t-butyl dicarbonate (1.58 g, 7.23 mmol) at room temperature. The resulting mixture was stirred for 30 minutes. Water (200 ml) was added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue so obtained was purified by chromatography on a silica gel column (100 g of silica gel, methylene chloride : ethyl acetate = 3:1 → 1:1), whereby the title compound (955 mg) was obtained as a colorless oil.

[0837]

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 3.12 (2H, t, J=5.9Hz),

3.77 (2H, t, J=5.9Hz), 4.00 (3H, s), 4.67 (2H, s),
7.57 (1H, d, J=8.1Hz), 7.98 (1H, d, J=8.1Hz).

[0838]

[Referential Example 134]

6-(t-Butoxycarbonyl)-2-[[4-(chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthylidene

To a solution of 6-(t-butoxycarbonyl)-2-methoxycarbonyl-5,6,7,8-tetrahydro-1,6-naphthylidene (955 mg) in tetrahydrofuran (20 ml), a 3N aqueous solution of sodium hydroxide (20 ml) was added at room temperature. After stirring for 2 hours, ammonium sulfate (16.0 g) was added to the reaction mixture. Concentrated hydrochloric acid was added to adjust its pH to 4, followed by extraction with chloroform (2 x 20 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, whereby the residue (874 mg), that is, 6-(t-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidene-2-carboxylic acid was obtained as a white solid. To a solution of the resulting residue in N,N-dimethylformamide (40 ml), methylene chloride (40 ml) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (1.42 g) were dissolved, followed by the addition of 1-(dimethylaminopropyl)-3-ethylcarbodiimide (785 mg) and 1-hydroxybenzotriazole (555 mg) at room temperature. Then, diisopropylethylamine (1.71 ml) was added at 0°C. After stirring overnight at room temperature, a 10% aqueous solution

of citric acid (200 ml) and methylene chloride (100 ml) were added to the reaction mixture to cause separation. The organic layer was extracted with methylene chloride (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (100 g of silica gel, methylene chloride : acetone = 10:1 → 5:1). The white solid thus obtained was reprecipitated in a methylene chloride-methanol-water system. After filtration and washing with water, the title compound (1.4 g) was obtained as a white solid.

[0839]

IR(KBr) cm^{-1} : 2978, 2924, 2846, 1697, 1637, 1577, 1479, 1454, 1432, 1365, 1340, 1238, 1166, 733, 577.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (9H, s), 2.92 (2H, t, $J=5.7\text{Hz}$), 3.11 (2H, br t, $J=4.4\text{Hz}$), 3.23 (2H, br t, $J=4.4\text{Hz}$), 3.74 (2H, t, $J=5.7\text{Hz}$), 3.78 (2H, br t, $J=4.4\text{Hz}$), 3.90 (2H, br t, $J=4.4\text{Hz}$), 4.59 (2H, s), 7.42 (1H, br d, $J=7.8\text{Hz}$), 7.47 (1H, br d, $J=7.8\text{Hz}$), 7.58 (1H, dd, $J=2.0, 8.8\text{Hz}$), 7.77 (1H, dd, $J=2.0, 8.5\text{Hz}$), 7.90 (1H, d, $J=2.0\text{Hz}$), 7.92-7.95 (2H, m), 8.30 (1H, br s).

MS (FAB) m/z : 571 [$(\text{M}+\text{H})^+$, Cl^{35}], 515 [$(\text{M}+\text{H})^+$ -isobutene(56), Cl^{35}].

Elementary analysis for $\text{C}_{28}\text{H}_{31}\text{ClN}_4\text{O}_5\text{S}$

Calculated: C, 58.89; H, 5.47; N, 9.81; Cl, 6.21; S, 5.61.

Found: C, 58.59; H, 5.61; N, 9.84; Cl, 6.53; S, 5.66.

[0840]

[Referential Example 135]

2-(t-Butoxycarbonylamino)-3-(t-butyldiphenylsiloxy)propanol

At room temperature, imidazole (6.43 g) was added to a solution of N-(t-butoxycarbonyl)-L-serine methyl ester (13.8 g) in N,N-dimethylformamide (140 ml), followed by the addition of t-butyldiphenylsilyl chloride (19.7 ml) at 0°C. The resulting mixture was stirred at room temperature for 39 hours. Ethyl acetate (200 ml) and water (600 ml) were added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, washed with saturated saline (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was dissolved in tetrahydrofuran (100 ml) and methanol (100 ml) without purification, followed by the addition of sodium borohydride (7.20 g) in portions at 0°C. After stirring at 0°C for 2 hours and then at room temperature for 1 hour, ethyl acetate (100 ml), an aqueous saturated solution of ammonium chloride (300 ml) and water (300 ml) were added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (500 g of silica gel, hexane : ethyl acetate = 10:1 → 1:1), whereby the title compound

(24.9 g) was obtained as a white solid.

[0841]

^1H -NMR (CDCl_3) δ : 1.07 (9H, s), 1.44 (9H, s), 2.39 (1H, br s), 3.63-3.85 (5H, m), 5.07 (1H, br s), 7.35-7.48 (6H, m), 7.60-7.67 (4H, m).

[0842]

[Referential Example 136]

2-(t-Butoxycarbonylamino)-3-(t-butyldiphenylsiloxy)propanal

To a solution of 2-(t-butoxycarbonylamino)-3-(t-butyldiphenylsiloxy)propanol (3.03 g) in methylene chloride (100 ml), Dess-Martin periodinane (3.60 g) was added at room temperature. The resulting mixture was stirred for 30 minutes. To the reaction mixture, a saturated aqueous solution (50 ml) of sodium bicarbonate and a 10% aqueous solution (50 ml) of sodium sulfite were added to cause separation. The water layer was extracted with diethyl ether (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (150 g of silica gel, hexane : ethyl acetate = 4:1 \rightarrow 3:1), whereby the title compound (2.97 g) was obtained as a colorless transparent oil.

[0843]

^1H -NMR (CDCl_3) δ : 1.03 (9H, s), 1.46 (9H, s), 3.93 (1H, dd, $J=3.9, 10.3\text{Hz}$), 4.18 (1H, d, $J=2.9, 10.3\text{Hz}$), 4.27-

4.35(1H,m), 5.33-5.43(1H,m), 7.32-7.48(6H,m), 7.55-7.63(4H,m), 9.66(1H,s).

[0844]

[Referential Example 137]

1-5-Bis(t-butoxycarbonyl)-2-(t-butyl diphenylsiloxy)methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of diisopropylamine (2.35 ml) in tetrahydrofuran (40 ml), n-butyl lithium (a 1.66 N hexane solution, 9.20 ml) was added at 0°C, followed by stirring for 30 minutes. To the reaction mixture, a solution of N-(t-butoxycarbonyl)-4-piperidone (2.77 g) in tetrahydrofuran (10 ml) was added at -78°C, and the mixture was stirred for 1.5 hours. To the reaction mixture, a solution of 2-(t-butoxycarbonylamino)-3-(t-butyl diphenylsiloxy)propanal (2.97 g) in tetrahydrofuran (10 ml) which had been cooled to -78°C was added dropwise. The mixture was heated gradually and stirred for 13 hours. Water (150 ml) and diethyl ether (350 ml) were added to the reaction mixture to cause separation. The water layer was extracted with diethyl ether (100 ml). The organic layers were combined, washed with water (100 ml) and saturated saline (3 x 100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was dissolved in methylene chloride (20 ml). Concentrated hydrochloric acid was added dropwise and the mixture was adjusted to pH 5, followed by stirring for 1 hour. Concentrated hydrochloric acid was further added dropwise to

adjust its pH to 4, followed by stirring for 1 hour. A saturated aqueous solution (50 ml) of sodium bicarbonate and methylene chloride (20 ml) were added to cause separation. The water layer was extracted with diethyl ether (2 x 50 ml). The organic layers were combined, washed with saturated saline (50 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (150 g of silica gel, hexane : ethyl acetate = 8:1 → 4:1), whereby the title compound (2.20 g) was obtained as a colorless transparent caramel-like substance.

[0845]

IR(KBr) cm^{-1} : 2931, 2856, 1738, 1697, 1473, 1427, 1392, 1367, 1350, 1331, 1232, 1167, 1144, 1109, 1066, 822, 739.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.08(9H,s), 1.43(9H,s), 1.49(9H,s), 2.89(2H,br s), 3.64(2H,br s), 4.32(2H,s), 4.85(2H,br s), 6.12(1H,s), 7.30-7.48(6H,m), 7.60-7.75(4H,m).

MS(FAB/m-NBA/NaCl) m/z : 613 [$(\text{M}+\text{Na})^+$].

[0846]

[Referential Example 138]

1,5-Bis(t-butoxycarbonyl)-2-hydroxymethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-(t-butylidiphenylsiloxy)methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (2.10 g) in pyridine (20 ml), a mixture

(5.0 ml) of hydrogen fluoride and pyridine was added at 0°C, followed by stirring at room temperature for 1 hour. After the reaction mixture was poured into ethyl acetate (50 ml) and ice water (300 ml) which had been stirred in advance, the resulting mixture was separated. The water layer was extracted with ethyl acetate (50 ml). The organic layers were combined, washed with a saturated aqueous solution (100 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (150 g of silica gel, hexane : ethyl acetate = 3:1), whereby the title compound (882 mg) was obtained as a colorless, transparent caramel-like substance.

[0847]

IR(KBr)cm⁻¹: 3432, 2976, 2931, 1736, 1695, 1419, 1365, 1350, 1323, 1234, 1167, 1144, 1105, 754.

¹H-NMR (CDCl₃) δ: 1.47(9H,s), 1.60(9H,s), 2.85(2H,br s), 3.45-3.70(1H,br), 3.64(2H,br s), 4.29(2H,s), 4.59(2H,d,J=7.3Hz), 6.01(1H,s).

MS (FAB/m-NBA/NaCl) m/z: 375 [(M+Na)⁺].

[0848]

[Referential Example 139]

1,5-Bis(t-butoxycarbonyl)-2-formyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-hydroxymethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

(14.0 mg) in methylene chloride (2.0 ml), Dess-Martin periodinane (34.0 mg) was added at room temperature. The resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture, ethyl acetate (10 ml), a 10% aqueous solution (10 ml) of sodium thiosulfate and an aqueous solution (10 ml) of sodium bicarbonate were added to cause separation. The water layer was extracted with ethyl acetate (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by thin-layer preparative chromatography on silica gel (hexane : ethyl acetate = 2:1), whereby the title compound (9.8 mg) was obtained as a colorless transparent caramel-like substance.

[0849]

IR(KBr) cm^{-1} : 2976, 2933, 1741, 1697, 1660, 1479, 1413, 1367, 1346, 1298, 1281, 1234, 1165, 1146, 1103, 895, 850, 768.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 1.63 (9H, s), 2.96 (2H, br t, $J=5.4\text{Hz}$), 3.68 (2H, br t, $J=5.4\text{Hz}$), 4.37 (2H, s), 6.97 (1H, s), 10.14 (1H, br s).

MS (FAB/m-NBA) m/z : 351 [$(\text{M}+\text{H})^+$], 295 [$(\text{M}+\text{H} - \text{isobutene}(56))^+$], 239 [$(\text{M}+\text{H}) - 2 \times \text{isobutene}(56))^+$].

[0850]

[Referential Example 140]

1,5-Bis(*t*-butoxycarbonyl)-2-[[4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-formyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (44.0 mg) in t-butanol (2.0 ml), 2-methyl-2-butene (150 ml) and an aqueous solution (6.0 ml) of sodium chlorite (102 mg) and sodium dihydrogenphosphate (135 mg) were added at room temperature. After stirring for 21 hours, the reaction mixture was added with diethyl ether (10 ml) and water (10 ml), followed by the addition of ammonium sulfate until saturation. The resulting mixture was separated, followed by extraction with diethyl ether (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure, whereby the residue, that is, 1,5-bis(t-butoxycarbonyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid was obtained as a white foamy substance. To a solution of the resulting residue in N,N-dimethylformamide (2.0 ml), methylene chloride (2.0 ml) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (55.0 mg) were dissolved, followed by the addition of 1-(dimethylaminopropyl)-3-ethyl carbodiimide (30.5 mg) and 1-hydroxybenzotriazole (21.5 mg) at room temperature. At 0°C, diisopropylethylamine (67.0 ml) was added thereto. After stirring overnight at room temperature, a 10% aqueous citric acid solution (10 ml) and methylene chloride (10 ml) were added to the reaction mixture to cause separation. The organic layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting

residue was purified by thin-layer preparative chromatography on silica gel (methylene chloride : acetone = 10:1) and the white solid thus obtained was reprecipitated in a methylene chloride-methanol-water system. After filtration and washing with water, the title compound (50.0 mg) was obtained as a colorless transparent caramel-like substance.

[0851]

IR (KBr) cm^{-1} : 2981, 2929, 2860, 1743, 1693, 1647, 1456, 1421, 1367, 1348, 1325, 1279, 1236, 1165, 1103, 955, 945, 729.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.32 (9H, s), 1.46 (9H, s), 2.83 (2H, br t, $J=5.6\text{Hz}$), 3.04 (2H, br), 3.17 (2H, br), 3.55 (2H, br), 3.62 (2H, br t, $J=5.6\text{Hz}$), 3.82 (2H, br), 4.25 (2H, s), 5.94 (1H, s), 7.59 (1H, dd, $J=2.0, 8.8\text{Hz}$), 7.76 (1H, dd, $J=1.7, 8.5\text{Hz}$), 7.87-7.98 (3H, m), 8.30 (1H, br s).

MS (FAB/m-NBA/NaCl) m/z : 681 [$(\text{M}+\text{Na})^+$], 518 [$(\text{M}+\text{Na}-\text{Boc}(100))^+$], 525 [$(\text{M}+\text{Na}-\text{Boc}(100)-\text{isobutene}(56))^+$].

[0852]

[Example 1]

1-[[(6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In saturated ethanol chloride (5 ml), 1-[[(6RS)-6-(N-tert-butoxycarbonylaminoethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (0.22 g) was dissolved, followed by stirring at room temperature for 90 minutes. The residue

obtained by distilling off the solvent under reduced pressure was recrystallized from a mixed solvent of ethanol and diethyl ether, whereby the title compound (0.14 g, 68%) was obtained.

[0853]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.30-1.50 (1H,m), 1.90-2.10 (2H,m), 2.40-2.60 (1H,m), 2.60-3.00 (5H,m), 3.03 (4H,m), 3.40-3.80 (4H,br), 7.00-7.10 (3H,m), 7.73 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.81 (1H,dd, $J=8.8, 1.5\text{Hz}$), 8.05 (3H,br), 8.18 (1H,d, $J=8.3\text{Hz}$), 8.20-8.30 (2H,m), 8.49 (1H,s).

MS (FAB) m/z : 498 $[(M+H)^+, \text{Cl}^{35}]$, 500 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{26}\text{H}_{28}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot 3/2\text{H}_2\text{O}$

Calculated: C, 55.61; H, 5.74; N, 7.48; Cl, 12.63; S, 5.71.

Found: C, 55.64; H, 5.53; N, 7.77; Cl, 12.79; S, 5.76.

[0854]

[Example 2]

1-[[(6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[[(6RS)-6-(N-tert-butoxycarbonylaminoethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0855]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.30-1.50 (1H,m), 2.00-2.10 (2H,m), 2.40-

2.60 (1H, m), 2.60-3.00 (7H, m), 3.00-3.20 (2H, m), 3.30-3.50 (2H, m), 3.82 (2H, m), 4.22 (2H, br), 7.00-7.10 (1H, m), 7.25 (2H, s), 7.73 (1H, dd, J=8.8, 2.4 Hz), 7.81 (1H, dd, J=8.8, 1.5 Hz), 8.00-8.40 (6H, m), 8.52 (1H, s), 11.08 (1H, br).

MS (FAB) m/z: 484 [(M+H)⁺, Cl³⁵], 486 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₃₀ClN₃O₂S·2HCl

Calculated: C, 56.07; H, 5.79; N, 7.54; Cl, 19.10; S, 5.76.

Found: C, 56.04; H, 5.79; N, 7.52; Cl, 18.95; S, 5.80.

[0856]

[Example 3]

1-[[[(2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[[[(2RS)-6-(N-tert-butoxycarbonylaminoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0857]

¹H-NMR (DMSO-d₆) δ: 1.30-1.50 (1H, m), 2.00-2.20 (1H, m), 2.20-2.40 (1H, m), 2.40-2.60 (1H, m), 2.75 (2H, m), 2.90-3.30 (7H, m), 3.60-3.70 (2H, m), 3.70-4.00 (4H, m), 7.04 (1H, d, J=7.8 Hz), 7.10-7.30 (2H, m), 7.74 (1H, m), 7.86 (1H, d, J=8.8 Hz), 8.20-8.50 (6H, m), 8.56 (1H, s), 10.69 (1H, br).

MS (FAB) m/z: 484 [(M+H)⁺, Cl³⁵], 486 [(M+H)⁺, Cl³⁷].

Elementary analysis for $C_{26}H_{30}ClN_3O_2S \cdot 2HCl \cdot 1/2H_2O$

Calculated: C, 55.18; H, 5.88; N, 7.42; Cl, 18.79; S, 5.66.

Found: C, 55.34; H, 5.70; N, 7.31; Cl, 18.76; S, 5.85.

[0858]

[Example 4]

1-[[(2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[[(2RS)-6-(N-tert-butoxycarbonylaminoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0859]

1H -NMR (DMSO- d_6) δ : 1.55(1H,m), 1.80-1.90(1H,m), 2.60-2.90(4H,m), 2.90-3.10(5H,m), 3.50-3.80(4H,m), 3.90(2H,s), 7.05(1H,d,J=7.8Hz), 7.10-7.20(2H,m), 7.71(1H,d,J=8.8Hz), 7.82(1H,d,J=8.3Hz), 8.10-8.40(6H,m), 8.50(1H,s).

MS (FAB) m/z: 498 [(M+H) $^+$, Cl 35], 500 [(M+H) $^+$, Cl 37].

Elementary analysis for $C_{26}H_{28}ClN_3O_3S \cdot 1.2HCl \cdot 0.8H_2O$

Calculated: C, 56.15; H, 5.58; N, 7.55; Cl, 14.02; S, 5.76.

Found: C, 55.93; H, 5.22; N, 7.37; Cl, 14.26; S, 5.70.

[0860]

[Example 5]

1-[(7-Aminomethylnaphthalen-2-yl)carbonyl]-4-[(6-

chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[[7-(N-tert-butoxycarbonylaminomethyl)naphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0861]

¹H-NMR (DMSO-d₆) δ: 3.10 (4H, br), 3.30-3.90 (4H, br), 4.18 (2H, s), 7.46 (1H, d, J=8.8Hz), 7.69 (1H, d, J=8.8Hz), 7.73 (1H, d, J=8.8Hz), 7.83 (1H, d, J=8.8Hz), 7.89 (1H, s), 7.90-8.00 (3H, m), 8.19 (1H, d, J=8.8Hz), 8.20-8.30 (2H, m), 8.50 (4H, br s).

MS (FAB) m/z: 494 [(M+H)⁺, Cl³⁵], 496 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₄ClN₃O₃S·HCl·3/4H₂O

Calculated: C, 57.41; H, 4.91; N, 7.72; Cl, 13.03; S, 5.89.

Found: C, 57.40; H, 4.87; N, 7.71; Cl, 13.09; S, 5.89.

[0862]

[Example 6]

1-[(7-Aminomethylnaphthalen-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[[7-(N-tert-butoxycarbonylaminomethyl)naphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0863]

¹H-NMR (DMSO-d₆) δ: 2.92 (2H, m), 3.22 (2H, m), 3.83 (2H, m), 4.20 (2H, d, J=5.4Hz), 4.51 (2H, br), 7.60-7.90 (4H, m), 7.90-

8.40 (7H, m), 8.52 (1H, s), 8.57 (3H, br), 11.52 (1H, br).

MS (FAB) m/z : 480 $[(M+H)^+, Cl^{35}]$, 482 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{26}H_{26}ClN_3O_2S \cdot 2HCl \cdot 1/4H_2O$

Calculated: C, 56.02; H, 5.15; N, 7.54; Cl, 19.08; S, 5.75.

Found: C, 55.88; H, 5.45; N, 7.34; Cl, 18.90; S, 5.69.

[0864]

[Example 7]

1-[(6-Aminomethylnaphthalen-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In tetrahydrofuran (5 ml), 2-(N-tert-butoxycarbonylaminomethyl)-6-methoxycarbonylnaphthalene (0.15 g) was dissolved, followed by the addition of 1N sodium hydroxide (0.70 ml). The resulting mixture was stirred at room temperature for 16 hours. After the reaction mixture was concentrated under reduced pressure, the concentrate was diluted with dichloromethane and added with dilute hydrochloric acid and the organic layer was collected. The organic layer thus obtained was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in N,N-dimethylformamide (5 ml), followed by the addition of 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (0.21 g), N-methylmorpholine (54.0 μ l), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (94.0 mg) and 1-hydroxybenzotriazole (77.0 mg). The resulting mixture was stirred at room temperature for 21 hours. The reaction mixture

was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), followed by the reaction in the same manner as in Example 1, whereby the title compound (77.0 g, 29%) was obtained as colorless crystals.

[0865]

¹H-NMR (DMSO-d₆) δ: 3.09(4H,br), 3.40-3.90(4H,br), 4.19(2H,s), 7.47(1H,d,J=8.3Hz), 7.66(1H,d,J=8.3Hz), 7.73(1H,d,J=9.3Hz), 7.83(1H,d,J=8.8Hz), 7.90-8.10(4H,m), 8.19(1H,d,J=8.8Hz), 8.20-8.30(2H,m), 8.40-8.60(4H,m).

MS (FAB) m/z: 494 [(M+H)⁺, Cl³⁵], 496 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₄ClN₃O₃S·HCl·3/4H₂O·1/5Et₂O

Calculated: C, 57.60; H, 5.14; N, 7.52; Cl, 12.69; S, 5.74.

Found: C, 57.64; H, 5.10; N, 7.12; Cl, 12.69; S, 5.82.

[0866]

[Example 8]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(isoquinolin-7-yl)carbonyl]piperazine hydrochloride

In 4N hydrochloric acid, methyl 7-isoquinolinecarboxylate (J. Org. Chem., 38(21), 3701, 1973) (206 mg) was dissolved, followed by heating under reflux for 4 hours. In the same manner as in Example 7, a reaction was effected using the residue

obtained by distilling off the solvent under reduced pressure and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound (298 mg, 62%) was obtained.

[0867]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.95-3.25 (4H, m), 3.40-3.60 (2H, m), 3.70-3.90 (2H, m), 7.73 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.84 (1H, d, $J=8.8\text{Hz}$), 8.05 (1H, d, $J=7.3\text{Hz}$), 8.20 (1H, d, $J=8.8\text{Hz}$), 8.25-8.35 (3H, m), 8.41 (1H, d, $J=6.4\text{Hz}$), 8.45 (1H, s), 8.52 (1H, s), 8.71 (1H, d, $J=6.4\text{Hz}$), 9.79 (1H, s).

MS (FAB) m/z : 465 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 467 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot 2.2\text{H}_2\text{O}$

Calculated: C, 53.18; H, 4.72; N, 7.75; Cl, 13.08; S, 5.92.

Found: C, 53.11; H, 4.70; N, 7.60; Cl, 13.01; S, 6.16.

[0868]

[Example 9]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(quinolyl-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using quinoline-2-carboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

[0869]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.05 (2H, m), 3.17 (2H, m), 3.62 (2H, m), 3.83 (2H, m), 7.61 (1H, d, $J=8.3\text{Hz}$), 7.60-7.80 (2H, m), 7.80-

7.90 (2H, m), 7.95 (1H, d, J=8.3Hz), 8.00 (1H, d, J=7.3Hz),
8.18 (1H, d, J=8.8Hz), 8.20-8.40 (2H, m), 8.43 (1H, d, J=8.3Hz),
8.51 (1H, s).

Elementary analysis for $C_{24}H_{20}ClN_3O_3S$

Calculated: C, 61.87; H, 4.33; N, 9.02; Cl, 7.61; S, 6.88.

Found: C, 61.76; H, 4.20; N, 8.73; Cl, 7.65; S, 6.99.

[0870]

[Example 10]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4-hydroxyquinolin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 7, a reaction was effected using 4-hydroxyquinoline-2-carboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0871]

1H -NMR (DMSO- d_6) δ : 3.00-3.30 (4H, br), 3.53 (2H, br), 3.77 (2H, br),
6.45 (1H, s), 7.48 (1H, t, J=7.3Hz), 7.70-7.90 (4H, m), 8.10-
8.40 (4H, m), 8.52 (1H, s).

MS (FAB) m/z: 482 [(M+H) $^+$, Cl 35], 484 [(M+H) $^+$, Cl 37].

Elementary analysis for $C_{24}H_{20}ClN_3O_4S \cdot 9/10HCl \cdot 1/3CH_3OH, 3/2H_2O$

Calculated: C, 52.90; H, 4.60; N, 7.61; Cl, 12.19; S, 5.80.

Found: C, 53.17; H, 4.59; N, 7.39; Cl, 12.31; S, 6.07.

[0872]

[Example 11]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(8-

hydroxyquinolin-7-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 7, a reaction was effected using 8-hydroxyquinoline-7-carboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0873]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.90-3.30 (4H, br), 3.35 (2H, br), 3.79 (2H, br), 7.39 (1H, d, $J=8.3\text{Hz}$), 7.53 (1H, d, $J=8.3\text{Hz}$), 7.60-7.90 (3H, m), 8.10-8.40 (3H, m), 8.50 (1H, s), 8.60 (1H, d, $J=7.8\text{Hz}$), 8.96 (1H, d, $J=4.4\text{Hz}$).

MS (FAB) m/z : 482 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 484 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_4\text{S}\cdot\text{HCl}\cdot\text{CH}_3\text{OH}\cdot 1/4\text{H}_2\text{O}$

Calculated: C, 54.11; H, 4.63; N, 7.57; Cl, 12.78; S, 5.78.

Found: C, 54.40; H, 4.84; N, 7.66; Cl, 13.04; S, 5.99.

[0874]

[Example 12]

1-[(Benzimidazol-5-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 7, a reaction was effected using methyl N-triphenylmethyl-5-benzimidazolecarboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0875]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.08 (4H, br), 3.30-4.00 (4H, br),

7.48 (1H, d, J=8.3Hz), 7.60-7.90 (4H, m), 8.10-8.30 (3H, m),
8.50 (1H, s), 9.51 (1H, s).

MS (FAB) m/z: 455 [(M+H)⁺, Cl³⁵], 457 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₁₉ClN₄O₃S·HCl·5/4H₂O

Calculated: C, 51.42; H, 4.41; N, 10.90; Cl, 13.80; S, 6.24.

Found: C, 51.53; H, 4.40; N, 10.71; Cl, 13.61; S, 6.40.

[0876]

[Example 13]

1-[(Benzimidazol-5-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

In the same manner as in Example 12, a reaction was effected using methyl N-triphenylmethyl-5-benzimidazolecarboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0877]

¹H-NMR (DMSO-d₆) δ: 1.67 (1H, m), 1.93 (1H, m), 3.20-3.90 (8H, m),
7.44 (1/2H, m), 7.54 (1/2H, m), 7.68 (1H, m), 7.80-8.00 (3H, m),
8.10-8.30 (3H, m), 8.49 (1/2H, s), 8.55 (1/2H, s), 9.56 and
9.57 (1H, each s).

MS (FAB) m/z: 469 [(M+H)⁺, Cl³⁵], 471 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₁ClN₄O₃S·HCl·0.3CH₃OH·H₂O

Calculated: C, 52.50; H, 4.76; N, 10.51; Cl, 13.30; S, 6.01.

Found: C, 52.31; H, 4.66; N, 10.50; Cl, 13.34; S, 6.01.

[0878]

[Example 14]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

[0879]

In the same manner as in Example 7, a reaction was effected using sodium thiazolo[5,4-c]pyridine-2-carboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0880]

¹H-NMR (DMSO-d₆) δ: 3.10-3.30(4H,m), 3.84(2H,m), 4.32(2H,m), 7.69(1H,dd,J=8.8,2.0Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.10-8.30(4H,m), 8.51(1H,s), 8.79(1H,d,J=5.9Hz), 9.62(1H,s).

MS (FAB) m/z: 473 [(M+H)⁺, Cl³⁵], 475 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₁H₁₇ClN₄O₃S₂·HCl

Calculated: C, 49.51; H, 3.56; N, 11.00; Cl, 13.92; S, 12.59.

Found: C, 49.45; H, 3.71; N, 11.20; Cl, 13.67; S, 12.55.

[0881]

[Example 15]

1-[(E)-4-Chlorostyrylsulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 7, a reaction was effected using sodium thiazolo[5,4-c]pyridine-2-carboxylate and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0882]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.30 (4H, m), 3.87 (2H, m), 4.35 (2H, m),
7.35 (1H, d, $J=15.6\text{Hz}$), 7.40-7.50 (3H, m), 7.79 (1H, d, $J=8.3\text{Hz}$),
8.22 (1H, d, $J=5.9\text{Hz}$), 8.77 (1H, d, $J=5.9\text{Hz}$), 9.59 (1H, s).

MS (FAB) m/z : 449 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 451 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{19}\text{H}_{17}\text{ClN}_4\text{O}_3\text{S}_2 \cdot 1/2\text{HCl}$

Calculated: C, 48.85; H, 3.78; N, 11.99; Cl, 11.38; S, 13.73.

Found: C, 49.18; H, 3.80; N, 12.20; Cl, 11.05; S, 13.84.

[0883]

[Example 16]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0884]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.82-2.88 (4H, m), 2.91-2.99 (4H, m), 3.28-3.36 (2H, m), 3.47-3.55 (4H, m), 4.02 (2H, br s), 6.58 (1H, s),
7.71 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.81 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.23-7.28 (3H, m), 8.49 (1H, s), 9.42 (2H, br s).

MS (FAB) m/z : 462 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 464 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{24}\text{Cl}_4\text{N}_3\text{O}_2\text{S}_2 \cdot 2\text{HCl} \cdot 1.5\text{H}_2\text{O}$

Calculated: C, 47.02; H, 5.20; Cl, 18.93; N, 7.48; S, 11.41.

Found: C, 47.18; H, 5.41; Cl, 18.59; N, 7.37; S, 11.33.

[0885]

[Referential Example 17]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[trans-3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example 1, a reaction was effected using 1-[trans-3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material, whereby the title compound was obtained.

[0886]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.95-3.10 (6H,m), 3.32-3.51 (3H,m), 3.60-3.80 (3H,m), 4.12 (2H,s), 6.75 (1H,d, $J=15.1\text{Hz}$), 7.19 (1H,s), 7.50 (1H,d, $J=15.1\text{Hz}$), 7.70 (1H,dd, $J=8.8, 2.4\text{Hz}$), 7.81 (1H,dd, $J=8.8, 2.0\text{Hz}$), 8.15 (1H,d, $J=8.8\text{Hz}$), 8.22 (1H,d, $J=2.0\text{Hz}$), 8.50 (1H,s), 9.53 (2H,br s).

MS (FAB) m/z : 502 $[(M+H)^+, \text{Cl}^{35}]$, 504 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{24}\text{ClN}_3\text{O}_3\text{S}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$

Calculated: C, 52.65; H, 4.79; Cl, 12.95; N, 7.67; S, 11.71.

Found: C, 52.36; H, 4.88; Cl, 12.63; N, 8.01; S, 11.39.

[0887]

[Example 18]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]piperazine hydrochloride

In the same manner as in Example 1, a reaction was effected using 1-[3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material, whereby the title compound was obtained.

[0888]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.80-3.60 (16H, m), 4.12 (2H, br s), 7.11 (1H, br s), 7.74 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.83 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.20 (1H, s), 8.25-8.30 (2H, m), 8.53 (1H, s), 9.67 (2H, br s).

MS (FAB) m/z : 504 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 506 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{26}\text{ClN}_3\text{O}_3\text{S}_2 \cdot 1.2\text{HCl} \cdot 1.3\text{H}_2\text{O}$

Calculated: C, 50.46; H, 5.26; Cl, 13.65; N, 7.36.

Found: C, 50.83; H, 5.26; Cl, 13.43; N, 6.97.

[0889]

[Example 19]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0890]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.90-2.07 (2H, m), 2.72-2.80 (2H, m), 2.82-3.21 (8H, m), 3.35 (2H, br s), 3.51 (2H, d, $J=11.5\text{Hz}$),

3.82 (2H, d, J=11.5Hz), 4.06 (2H, s), 6.66 (1H, s),
 7.74 (1H, dd, J=8.8, 1.5Hz), 7.85 (1H, dd, J=8.8, 1.5Hz),
 8.20 (1H, d, J=8.8Hz), 8.25-8.39 (2H, m), 8.55 (1H, s), 9.50 (2H, br
 s), 11.26 (1H, br s).

MS (FAB) m/z: 490 [(M+H)⁺, Cl³⁵], 492 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₈ClN₃O₂S₂·2HCl·1.6H₂O

Calculated: C, 48.71; H, 5.65; Cl, 17.97; N, 7.10; S, 10.84.

Found: C, 49.01; H, 5.77; Cl, 17.62; N, 6.96; S, 10.82.

[0891]

[Example 20]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-[(4,5,6,7-
 tetrahydrothieno[3,2-c]pyridin-2-
 yl)methyl]carbamoyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was
 obtained using 1-[N-[(5-tert-butoxycarbonyl-4,5,6,7-
 tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]carbamoyl]-4-
 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw
 material.

[0892]

¹H-NMR (DMSO-d₆) δ: 2.78-2.86 (2H, br s), 2.88-2.94 (4H, m),
 3.29-3.35 (2H, m), 3.37-3.42 (4H, m), 4.03 (2H, br s),
 4.19 (2H, d, J=5.4Hz), 6.62 (1H, s), 7.25 (1H, t, J=5.4Hz),
 7.72 (1H, dd, J=8.8, 2.0Hz), 7.82 (1H, dd, J=8.8, 2.0Hz),
 8.16 (1H, d, J=8.8Hz), 8.22-8.26 (2H, m), 8.50 (1H, s), 9.27 (2H, br
 s).

Elementary analysis for $C_{23}H_{25}ClN_4O_3S_2 \cdot HCl \cdot 1.3H_2O$

Calculated: C, 48.90; H, 5.10; Cl, 12.55; N, 9.92.

Found: C, 49.02; H, 5.20; Cl, 12.50; N, 9.76.

[0893]

[Example 21]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0894]

1H -NMR (DMSO- d_6) δ : 2.99-3.05 (2H, m), 3.08 (4H, t, $J=4.6$ Hz), 3.35-3.40 (2H, m), 3.71 (4H, t, $J=4.6$ Hz), 4.11 (2H, s), 7.17 (1H, s), 7.71 (1H, dd, $J=8.8, 2.0$ Hz), 7.82 (1H, dd, $J=8.8, 2.0$ Hz), 8.22-8.28 (3H, m), 8.50 (1H, s), 9.38 (2H, br s).

MS (FAB) m/z : 476 $[(M+H)^+, Cl^{35}]$, 478 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{22}H_{23}ClN_3O_3S_2 \cdot HCl \cdot 3/2H_2O$

Calculated: C, 48.98; H, 4.86; Cl, 13.14; N, 7.79; S, 11.89.

Found: C, 48.96; H, 4.67; Cl, 13.21; N, 7.74; S, 11.93.

[0895]

[Example 22]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-

yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 1, a reaction was effected using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine as a raw material, whereby the title compound was obtained.

[0896]

¹H-NMR (DMSO-d₆) δ: 1.22 (3H, t, J=7.0Hz), 2.38-2.58 (1H, m), 2.65-2.72 (1H, m), 3.04 (2H, br s), 3.29-3.43 (3H, m), 3.70 (1H, br s), 4.01-4.30 (6H, m), 5.18 (1H, br s), 7.27 (1H, s), 7.73 (1H, dd, J=8.8, 2.0Hz), 7.82 (1H, d, J=8.8Hz), 8.26 (1H, s), 8.29 (1H, s), 8.54 (1H, s), 9.59 (2H, br s).

MS (FAB) m/z: 548 [(M+H)⁺, Cl³⁵], 550 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₆N₃ClO₅S₂·1.2HCl·0.6H₂O

Calculated: C, 49.83; H, 4.75; Cl, 12.94; N, 6.97; S, 10.64.

Found: C, 49.62; H, 4.71; Cl, 13.30; N, 7.19; S, 10.56.

[0897]

[Example 23]

2-Carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In tetrahydrofuran (1 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (95 mg) was dissolved, followed by the addition of ethanol (2 ml) and 1N sodium hydroxide (3 ml). The resulting

mixture was heated under reflux for 30 minutes. To the reaction mixture, 4N hydrochloric acid (2 ml) was added and the precipitate thus obtained was collected by filtration, whereby the title compound (83 mg, 90%) was obtained as a colorless foam.

[0898]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.30-2.53 (1H,m), 2.58-2.69 (1H,m), 3.04 (2H,br s), 3.29-3.83 (4H,m), 4.07-4.32 (4H,m), 4.90-5.20 (1H,m), 7.03-7.30 (1H,m), 7.71 (1H,dd, $J=8.8, 2.4\text{Hz}$), 7.81 (1H,d, $J=8.8\text{Hz}$), 8.81 (1H,d, $J=8.8\text{Hz}$), 8.20-8.29 (2H,m), 8.52 (1H,s), 9.58 (2H,br s).

MS (FAB) m/z : 520 [$(\text{M}+\text{H})^+$, Cl^{35}], 522 [$(\text{M}+\text{H})^+$, Cl^{37}].

Elementary analysis for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{ClO}_5\text{S}_2 \cdot 1.2\text{HCl} \cdot 0.8\text{H}_2\text{O}$

Calculated: C, 47.78; H, 4.32; Cl, 13.49; N, 7.27; S, 11.09.

Found: C, 47.41; H, 4.36; Cl, 13.81; N, 7.14; S, 11.01.

[0899]

[Example 24]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine

To methanol (4 ml), a solution of 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyano-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine (41 mg) in dichloromethane (1 ml) was added, followed by the addition of hydroxylamine hydrochloride (28 mg) and triethylamine (0.55 ml). The resulting mixture was stirred at room temperature for 2 hours. The residue obtained by concentrating the reaction

mixture under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:3), whereby the title compound (14 mg, 32%) was obtained.

[0900]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.74-2.79 (2H, m), 3.06 (4H, s), 3.35-3.38 (2H, m), 3.71 (4H, s), 4.07 (2H, s), 5.32 (2H, s), 7.08 (1H, s), 7.71 (1H, dd, $J=8.8, 1.6\text{Hz}$), 7.81 (1H, dd, $J=8.8, 1.6\text{Hz}$), 8.16 (1H, s), 8.23-8.25 (2H, m), 8.33 (1H, br s), 8.49 (1H, s).

MS (FAB) m/z : 534 [(M+H) $^+$, Cl^{35}], 536 [(M+H) $^+$, Cl^{37}].

[0901]

[Example 25]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine hydrochloride

In the same manner as in Example 1, a reaction was effected using 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material, whereby the title compound was obtained.

[0902]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.83 (2H, br s), 2.99 (4H, br s), 3.30 (2H, br s), 3.54 (4H, br s), 4.00 (2H, s), 6.33 (1H, s), 7.70 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82 (1H, d, $J=8.8\text{Hz}$), 8.16 (1H, d, $J=8.8\text{Hz}$), 8.22 (1H, s), 8.26 (1H, d, $J=8.8\text{Hz}$),

8.50 (1H, s), 9.18 (2H, br s), 9.82 (1H, s).

MS (FAB) m/z: 491 [(M+H)⁺, Cl³⁵], 493 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₃N₄ClO₃S₂·HCl·0.3H₂O

Calculated: C, 49.59; H, 4.65; Cl, 13.31; N, 10.51; S, 12.03.

Found: C, 49.32; H, 4.63; Cl, 13.34; N, 10.81; S, 12.03.

[0903]

[Example 26]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-methyl-N-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine hydrochloride

In the same manner as in Example 1, a reaction was effected using 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-N-methylcarbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material, whereby the title compound was obtained.

[0904]

¹H-NMR (DMSO-d₆) δ: 2.83 (2H, d, J=5.4Hz), 2.97 (4H, br s), 3.10 (3H, s), 3.28-3.41 (6H, m), 4.00 (2H, s), 6.35 (1H, s), 7.72 (1H, dd, J=8.8, 2.0Hz), 7.81 (1H, dd, J=8.8, 2.0Hz), 8.17 (1H, d, J=8.8Hz), 8.23-8.31 (2H, m), 8.50 (1H, s), 9.28 (2H, br s).

MS (FAB) m/z: 505 [(M+H)⁺, Cl³⁵], 507 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₅N₄ClO₃S₂·1.1HCl·0.5H₂O

Calculated: C, 49.85; H, 4.93; Cl, 13.43; N, 10.11; S, 11.57.

Found: C, 49.55; H, 4.92; Cl, 13.23; N, 10.13; S, 11.83.

[0905]

[Example 27]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(1-pyrrolin-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

In N,N-dimethylformamide (20 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (400 mg) was dissolved, followed by the addition of triethylamine (0.16 ml) and 2-methoxypyrroline (464 mg). The resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure. To the residue, 1N hydrochloric acid was added and the precipitate thus formed was collected by filtration, whereby the title compound (411 mg, 88%) was obtained as a pale yellow foamy solid.

[0906]

¹H-NMR (DMSO-d₆) δ: 2.07-2.18 (2H, m), 2.90-3.11 (8H, m), 3.62 (2H, t, J=6.8 Hz), 3.72 (4H, br), 3.80 (2H, t, J=5.9 Hz), 3.99 (2H, t, J=5.9 Hz), 4.62 (1H, br s), 4.73 (1H, br s), 7.10 (1H, s), 7.50 (1H, s), 7.72 (1H, dd, J=8.8, 2.0 Hz), 7.82 (1H, dd, J=8.8, 2.0 Hz), 8.18 (1H, d, J=8.8 Hz), 8.22-8.28 (2H, m), 8.51 (1H, s), 10.37 (1H, br s), 10.53 (1H, br s).

MS (FAB) m/z: 542 [(M+H)⁺, Cl³⁵], 544 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₆H₂₇ClN₄O₃S₂·1.3HCl·0.4H₂O

Calculated: C, 52.25; H, 4.91; Cl, 13.64; N, 9.37; S, 10.73.

Found: C, 52.34; H, 5.03; Cl, 13.56; N, 9.36; S, 10.74.

[0907]

[Example 28]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0908]

¹H-NMR (DMSO-d₆) δ: 3.01 (2H, t, J=5.9Hz), 3.11 (4H, br), 3.44 (2H, br s), 3.74 (2H, br s), 4.32-4.46 (4H, m), 7.71 (1H, dd, J=8.8, 2.0Hz), 7.83 (1H, dd, J=8.8, 2.0Hz), 8.15 (1H, d, J=8.8Hz), 8.23 (1H, s), 8.26 (1H, d, J=8.8Hz), 8.30 (1H, s).

MS (FAB) m/z: 477 [(M+H)⁺, Cl³⁵], 479 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₁H₂₁ClN₄O₃S₂·HCl·0.2H₂O

Calculated: C, 48.78; H, 4.37; Cl, 13.71; N, 10.84; S, 12.40.

Found: C, 48.60; H, 4.50; Cl, 13.58; N, 10.62; S, 12.29.

[0909]

[Example 29]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride; and

1-[(6-carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In a similar manner to Referential Example 33 and Example 24 by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a raw material, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride and also 1-[(6-carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine were obtained.

[0910]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

[0911]

¹H-NMR (DMSO-d₆) δ: 2.77(2H, br s), 3.09(4H, br), 3.48(2H, t, J=5.4Hz), 3.73(2H, br s), 4.30-4.50(4H, m), 5.61(1H, br s), 7.71(1H, dd, J=8.8Hz, 2.0Hz), 7.82(1H, dd, J=8.8, 2.0Hz), 8.15(1H, d, J=8.8Hz), 8.22(1H, d, J=1.5Hz), 8.25(1H, d, J=8.8Hz), 8.50(1H, s), 8.53(1H, br s).

MS (FAB) m/z: 535 [(M+H)⁺, Cl³⁵], 537 [(M+H)⁺, Cl³⁷].

[0912]

1-[(6-Carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

[0913]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.75 (2H, br s), 3.09 (4H, br), 3.63 (2H, t, $J=5.9\text{Hz}$), 3.73 (2H, br s), 4.39 (2H, br s), 4.59 (2H, s), 6.17 (2H, s), 7.70 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.14 (1H, d, $J=8.8\text{Hz}$), 8.21 (1H, d, $J=1.5\text{Hz}$), 8.25 (1H, d, $J=8.8\text{Hz}$), 8.50 (1H, s).

MS (FAB) m/z : 520 $[(M+H)^+, \text{Cl}^{35}]$, 522 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{22}\text{ClN}_5\text{O}_4\text{S}_2 \cdot \text{H}_2\text{O}$

Calculated: C, 49.11; H, 4.50; N, 13.02.

Found: C, 48.98; H, 4.12; N, 12.83.

[0914]

[Example 30]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(1-pyrrolin-2-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example 27, the title compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a raw material.

[0915]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.07-2.15 (2H, m), 2.94-3.16 (8H, m),

3.63 (2H, t, J=7.3Hz), 3.75 (2H, br s), 3.90 (2H, br s), 4.39 (2H, br s), 4.93 (2H, s), 7.70 (1H, dd, J=8.8, 2.0Hz), 7.83 (1H, dd, J=8.8, 2.0Hz), 8.15 (1H, d, J=8.8Hz), 8.22 (1H, d, J=2.0Hz), 8.25 (1H, d, J=8.8Hz), 8.50 (1H, s).

MS (FAB) m/z: 544 [(M+H)⁺, Cl³⁵], 546 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₅H₂₆ClN₅O₃S₂·1.4HCl·CH₃OH

Calculated: C, 49.79; H, 5.05; Cl, 13.57; N, 11.17; S, 10.23.

Found: C, 49.44; H, 4.78; Cl, 13.63; N, 10.83; S, 10.15.

[0916]

[Example 31]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-formyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example 7, a reaction was effected using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride and formic acid as raw materials, whereby the title compound was obtained.

[0917]

¹H-NMR (DMSO-d₆) δ: 2.74-2.88 (2H, m), 3.10 (4H, br), 3.31 (2H, s), 3.66-3.86 (4H, m), 4.64-4.73 (2H, m), 7.69 (1H, dd, J=8.8, 2.0Hz), 7.82 (1H, dd, J=8.8, 2.0Hz), 8.14 (1H, d, J=8.8Hz), 8.15-8.22 (2H, m), 8.24 (1H, d, J=8.8Hz), 8.50 (1H, s).

MS (FAB) m/z: 505 [(M+H)⁺, Cl³⁵], 507 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₁ClN₄O₄S₂·1/5H₂O

Calculated: C, 51.95; H, 4.24; Cl, 6.97; N, 11.02; S, 12.61.

Found: C, 52.18; H, 4.30; Cl, 6.69; N, 10.71; S, 12.21.

[0918]

[Example 213]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In dichloromethane (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (400 mg) was suspended, followed by the addition of triethylamine (0.22 ml) and acetic acid (0.05 ml). The resulting mixture was stirred at room temperature for 5 minutes. To the reaction mixture, a 30% aqueous solution (0.08 ml) of formaldehyde and sodium triacetoxyborohydride (264 mg) were added. The resulting mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue. The resulting mixture was washed with water and saturated saline, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in a saturated ethanol hydrochloride solution (11 ml), followed by concentration under reduced pressure. The residue thus obtained was crystallized from hexane and ethyl acetate, whereby the title compound (298 mg, 71%) was obtained.

[0919]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.89 (3H, s), 3.10 (6H, br), 3.32-3.81 (4H, m),

4.30-4.81 (4H, m), 7.71 (1H, dd, J=8.8, 2.0 Hz),
 7.82 (1H, dd, J=8.8, 2.0 Hz), 8.15 (1H, d, J=8.8 Hz), 8.20-8.28 (2H, m),
 8.50 (1H, s), 11.28 (1H, br s).

MS (FAB) m/z: 491 [(M+H)⁺, Cl³⁵], 493 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₃ClN₄O₃S₂·HCl·0.6H₂O

Calculated: C, 49.09; H, 4.72; Cl, 13.17; N, 10.41; S, 11.91.

Found: C, 48.88; H, 4.78; Cl, 13.26; N, 10.42; S, 12.03.

[0920]

[Example 33]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridinium iodide

In N,N-dimethylformamide (20 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (200 mg) was dissolved, followed by the addition of methyl iodide (0.05 ml) and potassium carbonate (79.0 mg). The resulting mixture was stirred overnight at 80°C. The reaction mixture was concentrated under reduced pressure. Water was added to the residue and the precipitate so formed was collected by filtration. The precipitate was dissolved in a mixed solution (1:1) of dichloromethane and methanol. Ethyl acetate was added to the resulting solution and the precipitate thus formed was collected by filtration, whereby the title compound (144 mg, 56%) was obtained.

[0921]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.05-3.23 (12H, m), 3.77 (2H, t, $J=5.9\text{Hz}$), 4.40 (2H, br s), 4.79 (2H, br s), 7.71 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.83 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.20-8.27 (2H, m), 8.52 (1H, s).

MS (FD) m/z : 505 (M^+ , Cl^{35}), 507 (M^+ , Cl^{37}).

Elementary analysis for $\text{C}_{23}\text{H}_{26}\text{ClIN}_4\text{O}_3\text{S}_2 \cdot 1/2\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$

Calculated: C, 44.35; H, 4.47; N, 8.28.

Found: C, 44.52; H, 4.23; N, 8.01.

[0922]

[Example 34]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine N-oxide

In acetone (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (400 mg) was suspended, followed by the addition of a 1N aqueous solution (0.38 ml) of sodium hydroxide and a 30% aqueous solution (3.50 ml) of hydrogen peroxide. The resulting mixture was stirred at room temperature for 8 days. After the reaction mixture was concentrated under reduced pressure, the residue was purified by chromatography through a synthetic adsorbent ("Diaion (r) HP-20", trade name; water ~ water : acetonitrile = 2:5), whereby the title compound (84 mg, 39%) was obtained.

[0923]

¹H-NMR (DMSO-d₆) δ: 2.83-2.90 (1H,m), 3.10 (5H,br), 3.20-3.47 (4H,m), 3.61-3.83 (3H,m), 4.28-4.50 (3H,m), 4.78-4.85 (1H,m), 7.69 (1H,dd, J=8.8, 2.0Hz), 7.82 (1H,dd, J=8.8, 2.0Hz), 8.14 (1H,d, J=8.8Hz), 8.19-8.27 (2H,m), 8.50 (1H,s).

MS (FD) m/z: 506 (M+, Cl³⁵), 508 (M+, Cl³⁷).

[0924]

[Example 35]

2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

To trifluoroacetic acid (1 ml), a solution of 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (303 mg) dissolved in dichloromethane (1 ml) was added, followed by concentration under reduced pressure. The precipitate thus formed was collected by filtration and washed with diethyl ether, whereby the title compound (263 mg, 83%) was obtained.

[0925]

¹H-NMR (DMSO-d₆) δ: 2.39-2.70 (2H,m), 2.92-3.06 (2H,m), 3.42-3.77 (4H,m), 4.25-4.50 (7/2H,m), 4.97 (1/2H,br s), 5.35-5.44 (1/2H,m), 6.14 (1/2H,br s), 7.30-7.39 (1H,m), 7.66-7.73 (2H,m), 7.77-7.82 (1H,m), 8.16 (1H,d, J=8.8Hz), 8.21-8.28 (2H,m), 8.49 (1H,s), 9.26 (2H,br s).

MS (FAB) m/z : 520 $[(M+H)^+, Cl^{35}]$, 522 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{22}H_{22}ClN_5O_4S_2 \cdot CF_3CO_2H \cdot 0.6H_2O$

Calculated: C, 44.29; H, 3.73; Cl, 5.40; F, 9.55; N, 10.67; S, 9.77.

Found: C, 44.59; H, 3.79; Cl, 5.26; F, 9.54; N, 10.28; S, 9.72.

[0926]

[Example 36]

2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 32, the title compound was obtained using 2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate as a raw material.

[0927]

1H -NMR (DMSO- d_6) δ : 2.37-2.70 (2H, m), 2.91 (3H, s), 3.00-3.78 (6H, m), 4.28-4.77 (7/2H, m), 4.97 (1/2H, br s), 5.40-5.50 (1/2H, m), 6.14 (1/2H, br s), 7.32-7.40 (1H, m), 7.68-7.75 (2H, m), 7.77-7.83 (1H, m), 8.15 (1H, d, $J=8.8$ Hz), 8.21-8.28 (2H, m), 8.49 (1H, s).

MS (FAB) m/z : 534 $[(M+H)^+, Cl^{35}]$, 536 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{23}H_{24}ClN_5O_4S_2 \cdot HCl \cdot 2.5H_2O$

Calculated: C, 44.88; H, 4.91; Cl, 11.52; N, 11.38; S, 10.42.

Found: C, 44.83; H, 4.89; Cl, 11.65; N, 11.31; S, 10.46.

[0928]

[Referential Example 37]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

The crude product, which had been obtained by the reaction in the same manner as in Example 32 by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (132 mg) and glyoxylic hydrate (82 mg) as raw materials, was suspended in tetrahydrofuran (50 ml). Triethylamine (0.22 ml) and ethyl chloroformate (0.03 ml) were added to the resulting suspension under ice cooling, followed by stirring at room temperature for 15 minutes. To the reaction mixture, sodium borohydride (50 mg) and water (10 ml) were added to the reaction mixture and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane, washed with saturated saline and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:3), followed by dissolution in saturated ethanol hydrochloride (1 ml). The resulting solution was then concentrated under reduced pressure. The concentrate was pulverized and washed in ethyl acetate, whereby

the title compound (52 mg, 33%) was obtained.

[0929]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.11 (4H, br s), 3.20-3.57 (6H, m), 3.69-3.87 (4H, m), 4.34-4.82 (4H, m), 5.38 (1H, br s), 7.71 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.22 (1H, s), 8.25 (1H, d, $J=8.8\text{Hz}$), 8.50 (1H, s), 10.48 (1H, br s).

MS (FAB) m/z : 521 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 523 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[0930]

In the same manner as in Example 32, the compounds of Examples 38, 39 and 40 were obtained, respectively by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a raw material.

[0931]

[Example 38]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

[0932]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.07-3.17 (6H, m), 3.63 (2H, t, $J=6.3\text{Hz}$), 3.74 (2H, br s), 4.39 (2H, br s), 4.58 (2H, s), 4.61 (2H, s), 7.50-7.64 (1H, m), 7.67-7.73 (2H, m), 7.82 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.97 (1H, m), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.22 (1H, d, $J=1.5\text{Hz}$), 8.25 (1H, d, $J=8.8\text{Hz}$), 8.50 (1H, s), 8.69 (1H, d, $J=4.9\text{Hz}$).

MS (FAB) m/z : 568 $[(M+H)^+, Cl^{35}]$, 570 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{27}H_{26}ClN_5O_3S_2 \cdot 2HCl \cdot 0.8H_2O$

Calculated: C, 49.48; H, 4.55; Cl, 16.23; N, 10.68; S, 9.78.

Found: C, 49.72; H, 4.48; Cl, 16.31; N, 10.86; S, 9.53.

[0933]

[Example 39]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-3-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

[0934]

1H -NMR (DMSO- d_6) δ : 3.03-3.27 (6H, m), 3.40-3.81 (4H, m), 3.74 (2H, br s), 4.40 (2H, br s), 4.50 (2H, s), 4.70 (2H, s), 7.70 (1H, dd, $J=8.8, 2.4$ Hz), 7.82 (1H, d, $J=8.8$ Hz), 8.15 (1H, d, $J=8.8$ Hz), 8.22 (1H, s), 8.25 (1H, d, $J=8.8$ Hz), 8.50 (1H, s), 8.73 (1H, d, $J=7.8$ Hz), 8.93 (1H, d, $J=4.4$ Hz).

MS (FAB) m/z : 568 $[(M+H)^+, Cl^{35}]$, 570 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{27}H_{26}ClN_5O_3S_2 \cdot 2.9HCl \cdot 4.5H_2O$

Calculated: C, 42.96; H, 5.06; Cl, 18.32; N, 9.28.

Found: C, 42.97; H, 4.84; Cl, 18.19; N, 9.23.

[0935]

[Example 40]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

[0936]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.11 (4H, br s), 3.19 (2H, br s), 3.64 (2H, br s), 3.74 (2H, br s), 4.41 (2H, br s), 4.49 (2H, s), 4.80 (2H, s), 7.69 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.82 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.21 (1H, d, $J=2.0\text{Hz}$), 8.25 (1H, d, $J=8.8\text{Hz}$), 8.41 (2H, d, $J=6.3\text{Hz}$), 8.50 (1H, s), 9.04 (2H, d, $J=6.3\text{Hz}$).

MS (FAB) m/z : 568 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 570 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{27}\text{H}_{26}\text{ClN}_5\text{O}_3\text{S}_2 \cdot 2.7\text{HCl} \cdot 6.0\text{H}_2\text{O}$

Calculated: C, 41.86; H, 5.30; Cl, 16.93; N, 9.04; S, 8.28.

Found: C, 42.05; H, 4.98; Cl, 16.92; N, 9.37; S, 8.61.

[0937]

[Example 41]

1-[(E)-4-Chlorostyrylsulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(E)-4-chlorostyrylsulfonyl]piperazine as a raw material.

[0938]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.04 (2H, br s), 3.23 (4H, br), 3.47 (2H, br s), 3.77 (2H, br s), 4.35-4.50 (2H, m), 7.33 (1H, d, $J=15.6\text{Hz}$), 7.43 (1H, d, $J=15.6\text{Hz}$), 7.49 (1H, d, $J=8.3\text{Hz}$), 7.79 (1H, d, $J=8.3\text{Hz}$), 9.57 (2H, br s).

MS (FAB) m/z : 453 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 455 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{19}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}_2 \cdot \text{HCl} \cdot 0.3\text{H}_2\text{O}$

Calculated: C, 46.12; H, 4.60; Cl, 14.33; N, 11.32; S, 12.96.

Found: C, 46.42; H, 4.66; Cl, 14.38; N, 11.02; S, 13.02.

[0939]

Example 42

1-[(E)-4-Chlorostyrylsulfonyl]-4-[6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example 32, the title compound was obtained using 1-[(E)-4-chlorostyrylsulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a raw material.

[0940]

¹H-NMR (DMSO-d₆) δ: 2.92 (3H, s), 3.01-3.32 (6H, br), 3.35-3.88 (4H, m), 4.29-4.84 (4H, m), 7.33 (1H, d, J=15.6Hz), 7.49 (1H, d, J=15.6Hz), 7.49 (1H, d, J=8.3Hz), 7.79 (1H, d, J=8.3Hz), 11.31 (1H, br s).

MS (FAB) m/z: 467 [(M+H)⁺, Cl³⁵], 469 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₀H₂₃ClN₄O₃S₂·HCl·0.2H₂O

Calculated: C, 47.37; H, 4.85; Cl, 13.98; N, 11.05; S, 12.65.

Found: C, 47.30; H, 4.92; Cl, 14.05; N, 11.03; S, 12.49.

[0941]

[Example 43]

(3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]pyrrolidine hydrochloride

In the same manner as in Example 1, the title compound was obtained using (3S)-1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine as a raw material.

[0942]

$[\alpha]_D = -69.72^\circ$ (25°C, c=1.00, CH₃OH).

¹H-NMR (DMSO-d₆ at 100°C) δ : 1.88-1.89 (1H, m), 2.10-2.25 (1H, m), 3.02-3.07 (2H, m), 3.10-3.50 (6H, m), 4.02 (1H, s), 4.12 (2H, s), 4.45 (2H, s), 7.12 (1H, s), 7.65 (1H, d, J=8.3Hz), 7.91 (1H, d, J=8.3Hz), 8.10 (1H, d, J=8.3Hz), 8.14 (1H, s), 8.16 (1H, d, J=8.3Hz), 8.18 (1H, br s), 8.48 (1H, s), 9.65 (2H, br s).
MS (FD) m/z: 461 (M⁺, Cl³⁵), 463 (M⁺, Cl³⁷).

Elementary analysis for C₂₂H₂₄ClN₃O₂S₂·2.1HCl·H₂O

Calculated: C, 47.47; H, 5.09; Cl, 19.74; N, 7.55; S, 11.52.
Found: C, 47.55; H, 5.13; Cl, 19.85; N, 7.45; S, 11.48.

[0943]

[Example 44]

(3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]pyrrolidine hydrochloride

In the same manner as in Example 1, the title compound was obtained using (3S)-1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine as a raw

material.

[0944]

$[\alpha]_D = -62.70^\circ$ (25°C, $c=1.00$, CH_3OH).

$^1\text{H-NMR}$ (DMSO-d_6 at 100°C) δ : 1.82-1.90 (1H, m), 1.96-2.05 (1H, m), 3.05 (2H, t, $J=6.0\text{Hz}$), 3.42-3.57 (2H, m), 3.60-3.72 (2H, m), 3.84-3.90 (1H, m), 4.12 (2H, s), 4.45 (2H, s), 7.25 (1H, s), 7.64 (1H, dd, $J=8.3, 1.6\text{Hz}$), 7.90 (1H, dd, $J=8.3, 1.6\text{Hz}$), 7.97 (1H, d, $J=5.6\text{Hz}$), 8.08 (1H, d, $J=8.7\text{Hz}$), 8.12 (1H, s), 8.14 (1H, d, $J=8.7\text{Hz}$), 8.47 (1H, s), 9.55 (2H, br s).

MS (FAB) m/z : 476 $[(M+H)^+, \text{Cl}^{35}]$, 478 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{22}\text{H}_{22}\text{ClN}_3\text{O}_3\text{S}_2 \cdot \text{HCl}$

Calculated: C, 51.56; H, 4.52; Cl, 13.84; N, 8.20; S, 12.51.

Found: C, 51.25; H, 4.61; Cl, 13.68; N, 7.98; S, 12.36.

[0945]

[Example 45]

(3S)-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]amino]pyrrolidine hydrochloride

In the same manner as in Example 1, the title compound was obtained using (3S)-3-[[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]amino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine as a raw material.

[0946]

$[\alpha]_D = +34.82^\circ$ (25°C, $c=1.00$, CH_3OH).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.98-2.20 (2H, m), 2.99-3.04 (2H, m), 3.19-

3.26 (1H, m), 3.30-3.50 (3H, m), 3.61-3.72 (1H, m), 3.52-3.60 (1H, m), 4.13 (2H, s), 4.29 (2H, s), 7.09 (1H, s), 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.89 (1H, dd, J=8.8, 2.0 Hz), 8.17 (1H, d, J=8.8 Hz), 8.25 (1H, d, J=2.0 Hz), 8.30 (1H, s), 8.57 (1H, s), 9.55 (2H, br s), 9.7-10.0 (1H, m).

MS (FD) m/z: 461 (M⁺, Cl³⁵), 463 (M⁺, Cl³⁷).

Elementary analysis for C₂₂H₂₄ClN₃O₂S₂·2HCl·0.2H₂O

Calculated: C, 49.06; H, 4.94; Cl, 19.75; N, 7.80; S, 11.91.

Found: C, 48.88; H, 4.97; Cl, 19.65; N, 7.67; S, 11.84.

[0947]

[Example 46]

(3S)-3-[(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine hydrochloride

In the same manner as in Example 1, the title compound was obtained using (3S)-3-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine as a raw material.

[0948]

[α]_D=+33.56° (25°C, c=1.00, CH₃OH).

¹H-NMR (DMSO-d₆) δ: 1.85-1.95 (1H, m), 1.95-2.05 (1H, m), 3.04 (2H, m), 3.24-3.40 (1H, m), 3.41-3.53 (3H, m), 4.04-4.24 (3H, m), 7.34 (1H, s), 7.67 (1H, d, J=8.8 Hz), 7.84 (1H, d, J=8.8 Hz), 8.03 (1H, d, J=8.8 Hz), 8.17 (1H, s), 8.22 (1H, d, J=8.8 Hz), 8.27 (1H, d, J=5.7 Hz), 8.50 (1H, s),

9.59(1H, br s), 9.71(1H, br s).

MS (FD) m/z: 476 [(M+H)⁺, Cl³⁵], 478 [(M+H)⁺, Cl³⁷].

[0949]

[Example 48]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]homopiperazine hydrochloride

In the same manner as in Example 1, the title compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine as a raw material.

[0950]

¹H-NMR (DMSO-d₆) δ: 1.83(2H, br s), 3.04(2H, t, J=5.4Hz), 3.30-3.59(6H, m), 3.60-3.88(4H, m), 4.14(2H, s), 7.20(1H, br s), 7.69(1H, dd, J=8.8, 2.0Hz), 7.84(1H, d, J=8.8Hz), 8.10(1H, d, J=8.8Hz), 8.17-8.21(2H, m), 8.50(1H, s), 9.57(2H, br s).

MS (FAB) m/z: 490 [(M+H)⁺, Cl³⁵], 492 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₅ClN₃O₃S₂·1.1HCl·0.2H₂O

Calculated: C, 51.66; H, 4.99; Cl, 13.92; N, 7.86.

Found: C, 51.46; H, 4.61; Cl, 13.55; N, 8.05.

[0951]

[Example 48]

4-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-[(4,5,6,7-

tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperidine
hydrochloride

In the same manner as in Example 7 or 1, a reaction was effected using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-carboxylic acid (WO94/21599) and 4-[(6-chloronaphthalen-2-yl)sulfonamido]piperidine trifluoroacetate as raw materials, whereby the title compound was obtained.

[0952]

¹H-NMR (DMSO-d₆) δ: 1.26-1.38 (2H,m), 1.58-1.65 (2H,m), 2.93-3.13 (4H,m), 3.29-3.40 (3H,m), 3.90-4.05 (2H,m), 4.11 (2H,s), 7.16 (1H,s), 7.68 (1H,dd, J=8.0, 2.0Hz), 7.92 (1H,dd, J=8.8, 2.0Hz), 8.07 (1H,d, J=7.3Hz), 8.13 (2H,d, J=8.8Hz), 8.20 (1H,d, J=7.3Hz), 8.23 (1H,s), 8.51 (1H,s), 9.71 (2H,br s).

MS (FAB) m/z: 490 [(M+H)⁺, Cl³⁵], 492 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₃H₂₅ClN₃O₃S₂·2.4HCl·3H₂O

Calculated: C, 43.67; H, 5.32; Cl, 19.05; N, 6.64.

Found: C, 43.85; H, 5.10; Cl, 19.07; N, 6.63.

[0953]

[Example 49]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethylbenzofuran-2-yl)carbonyl]piperazine

In the same manner as in Example 24, the title compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-cyanobenzofuran-2-yl)carbonyl]piperazine as a raw material.

[0954]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.11 (4H, s), 3.83 (4H, br), 5.90 (2H, br s), 7.34 (1H, s), 7.64-7.75 (3H, m), 7.83 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.89 (1H, s), 8.17 (1H, d, $J=8.8\text{Hz}$), 8.23 (1H, d, $J=1.5\text{Hz}$), 8.26 (1H, d, $J=8.8\text{Hz}$), 8.51 (1H, s), 9.77 (1H, s).

MS (FAB) m/z : 513 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 515 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{24}\text{H}_{21}\text{ClN}_4\text{O}_5\text{S} \cdot 1/5\text{H}_2\text{O}$

Calculated: C, 55.80; H, 4.18; Cl, 6.86; N, 10.70; S, 6.21.

Found: C, 55.65; H, 4.25; Cl, 6.81; N, 10.70; S, 6.37.

[0955]

[Example 50]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-aminohydroxyiminomethylbenzothiophen-2-yl)carbonyl]piperazine

In the same manner as in Example 24, the title compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyanobenzothiophen-2-yl)carbonyl]piperazine as a raw material.

[0956]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.11 (4H, s), 3.77 (4H, s), 5.87 (2H, br s), 7.67 (1H, s), 7.71 (1H, d, $J=2.0\text{Hz}$), 7.75 (1H, d, $J=8.8\text{Hz}$), 7.83 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.94 (1H, d, $J=8.8\text{Hz}$), 8.15 (1H, s), 8.17 (1H, d, $J=8.8\text{Hz}$), 8.25 (1H, d, $J=8.8\text{Hz}$), 8.29 (1H, d, $J=8.3\text{Hz}$), 8.50 (1H, s), 9.68 (1H, s).

MS (FAB) m/z : 529 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 531 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $C_{24}H_{21}N_4ClO_4S_2 \cdot 0.3H_2O$

Calculated: C, 53.94; H, 4.07; N, 10.48.

Found: C, 54.22; H, 4.17; N, 10.23.

[0957]

[Example 51]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]piperazine hydrochloride

[0958]

In the same manner as in Example 1, the title compound was obtained using 1-[(2-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0959]

1H -NMR (DMSO- d_6) δ : 2.89-3.29 (4H, m), 3.20-3.83 (8H, m), 4.25 (2H, s), 7.10-7.25 (3H, m), 7.71 (1H, d, $J=8.3$ Hz), 7.81 (1H, d, $J=8.3$ Hz), 8.17 (1H, d, $J=8.8$ Hz), 8.15-8.25 (2H, m), 8.49 (1H, s), 9.54 (2H, br s).

MS (FAB) m/z : 470 $[(M+H)^+, Cl^{35}]$, 472 $[(M+H)^+, Cl^{37}]$.

Elementary analysis for $C_{24}H_{24}ClN_3O_3S \cdot HCl \cdot 2.0H_2O$

Calculated: C, 53.14; H, 5.39; Cl, 13.07; N, 7.75; S, 5.91.

Found: C, 53.43; H, 5.43; Cl, 13.15; N, 8.07; S, 5.55.

[0960]

[Example 52]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(2-methyl-1,2,3,4-

tetrahydroisoquinolin-6-yl)carbonyl]piperazine
hydrochloride

In the same manner as in Example 32, a reaction was effected using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]piperazine hydrochloride as a raw material, whereby the title compound was obtained.

[0961]

¹H-NMR (DMSO-d₆) δ: 2.88 (3H, s), 2.90-3.80 (13H, m), 4.12-4.56 (1H, m), 7.19 (1H, s), 7.20 (2H, d, J=6.8 Hz), 7.72 (1H, dd, J=8.8, 2.0 Hz), 7.81 (1H, d, J=8.8 Hz), 8.17 (1H, d, J=8.8 Hz), 8.24-8.28 (2H, m), 8.49 (1H, s), 10.93 (1H, br s).

MS (FAB) m/z: 484 [(M+H)⁺, Cl³⁵], 486 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₄ClN₃O₃S·HCl·2.3H₂O

Calculated: C, 53.44; H, 5.67; Cl, 12.62; N, 7.48; S, 5.71.

Found: C, 53.71; H, 5.81; Cl, 12.37; N, 7.26; S, 5.62.

[0962]

[Example 53]

6-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide

In the same manner as in Example 33, the title compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]piperazine hydrochloride as a raw material.

[0963]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.90-3.85 (18H, m), 4.61 (2H, s),
 7.19 (1H, d, $J=7.8\text{Hz}$), 7.24 (1H, d, $J=7.8\text{Hz}$), 7.28 (1H, s),
 7.72 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.81 (1H, d, $J=8.8\text{Hz}$),
 8.17 (1H, d, $J=8.8\text{Hz}$), 8.20-8.31 (2H, m), 8.50 (1H, s).

Elementary analysis for $\text{C}_{26}\text{H}_{29}\text{ClIN}_3\text{O}_3\text{S}\cdot\text{H}_2\text{O}$

Calculated: C, 48.49; H, 4.85; N, 6.53.

Found: C, 48.66; H, 4.96; N, 6.39.

[0964]

[Example 54]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

A reaction was effected in the same manner as in Example 7 by using 1-[(5-chloroindol-2-yl)sulfonyl]piperazine and lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxylate as raw materials, whereby the title compound was obtained as brown amorphous.

[0965]

$^1\text{H-NMR}$ (CDCl_3) δ : 2.49 (3H, s), 2.78-2.83 (2H, m), 2.85-2.94 (2H, m),
 3.15-3.28 (4H, br), 3.67 (2H, s), 3.82-3.95 (2H, br), 4.50-
 4.65 (2H, br), 6.96 (1H, d, $J=2.0\text{Hz}$), 7.32 (1H, dd, $J=8.8, 2.0\text{Hz}$),
 7.36 (1H, d, $J=8.8\text{Hz}$), 7.67 (1H, s), 8.71 (1H, br).

MS (FAB) m/z : 480 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 482 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{20}\text{H}_{22}\text{ClN}_5\text{O}_3\text{S}_2\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 44.64; H, 4.76; Cl, 13.18; N, 13.02; S, 11.92.

Found: C, 44.69; H, 4.72; Cl, 13.36; N, 12.76; S, 11.76.

[0966]

In a similar manner to Example 54, the compounds shown in Examples 55 to 60 were synthesized.

[0967]

[Example 55]

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

[0968]

¹H-NMR (DMSO-d₆) δ: 2.50-2.63 (3H,m), 2.65-2.74 (2H,m), 2.92 (3H,s), 3.00-3.14 (2H,m), 3.22-3.42 (2H,m), 3.63-3.78 (2H,m), 4.23-4.29 (1H,m), 4.35-4.47 (1H,m), 4.64-4.80 (1H,m), 4.97-5.02 (1/2H,m), 5.45-5.51 (1H,m), 6.13-6.17 (1/2H,m), 7.02 (1H,br), 7.32 (1H,dd, J=8.8, 2.0Hz), 7.47 (1H,d, J=8.3Hz), 7.77 (1H,br), 8.07-8.16 (1H,m), 12.41 (1H,s).

MS (FAB) m/z: 537 [(M+H)⁺, Cl³⁵], 539 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₂H₂₅ClN₆O₄S₂·HCl·1.7H₂O

Calculated: C, 43.74; H, 4.90; Cl, 11.74; N, 13.91; S, 10.62.

Found: C, 44.02; H, 5.07; Cl, 11.83; N, 13.59; S, 10.52.

[0969]

[Example 56]

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-

yl)carbonyl]piperazine hydrochloride

[0970]

^1H -NMR (DMSO- d_6) δ : 2.65 (3H, d, $J=4.5\text{Hz}$), 2.85-3.22 (7H, m), 3.22-3.38 (2H, m), 3.66 (1H, d, $J=12.2\text{Hz}$), 3.55-3.68 (2H, m), 4.17-4.40 (3H, m), 4.55-4.68 (1H, m), 6.99 (1H, d, $J=2.0\text{Hz}$), 7.27-7.31 (2H, m), 7.48 (1H, d, $J=8.8\text{Hz}$), 7.77 (1H, d, $J=2.0\text{Hz}$), 8.09 (1H, br s), 10.60 (1H, br s), 12.41 (1H, s).

MS (FAB) m/z : 536 $[(M+H)^+, \text{Cl}^{35}]$, 538 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{23}\text{H}_{26}\text{ClN}_5\text{O}_4\text{S}_2 \cdot 1.3\text{HCl} \cdot 0.6\text{H}_2\text{O} \cdot 1.5\text{EtOH}$

Calculated: C, 47.07; H, 5.70; Cl, 12.29; N, 10.56; S, 9.67.

Found: C, 46.68; H, 5.63; Cl, 12.16; N, 10.20; S, 10.06.

[0971]

[Example 57]

1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0972]

^1H -NMR (DMSO- d_6) δ : 2.91 (3H, s), 3.11 (2H, br), 3.25-3.90 (4H, m), 3.76 (2H, br), 5.35-4.80 (2H, br), 4.41 (2H, br), 7.46 (1H, d, $J=8.8\text{Hz}$), 7.73 (1H, s), 7.84 (1H, d, $J=8.8\text{Hz}$), 7.96 (1H, s), 11.48 (1H, br).

MS (FAB) m/z : 481 $[(M+H)^+, \text{Cl}^{35}]$, 483 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{20}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}_2 \cdot 1.1\text{HCl} \cdot 0.3\text{H}_2\text{O}$

Calculated: C, 45.63; H, 4.35; Cl, 14.14; N, 10.64; S, 12.18.

Found: C, 45.81; H, 4.29; Cl, 13.93; N, 10.44; S, 12.26.

[0973]

[Example 58]

1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

[0974]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.91(3H,s), 3.00-3.55(7H,m), 3.60-3.85(3H,m), 4.42(3H,br), 4.67(1H,br), 7.46(1H,d,J=8.8Hz), 7.73(1H,s), 7.84(1H,d,J=8.8Hz), 7.96(1H,s), 11.48(1H,br).

MS (FAB) m/z : 481 [(M+H) $^+$, Cl 35], 483 [(M+H) $^+$, Cl 37].

Elementary analysis for $\text{C}_{20}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}_2 \cdot \text{HCl} \cdot 0.17\text{H}_2\text{O}$

Calculated: C, 46.15; H, 4.33; Cl, 13.62; N, 10.76; S, 12.32.

Found: C, 46.45; H, 4.41; Cl, 13.61; N, 10.58; S, 12.02.

[0975]

[Example 59]

1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

[0976]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.91(3H,s), 2.98-3.90(10H,m), 4.24-4.77(4H,m), 7.60(1H,d,J=8.8Hz), 8.05(1H,s), 8.10-8.21(2H,m), 11.72(1H,br s).

MS (FAB) m/z : 497 [(M+H) $^+$, Cl 35], 499 [(M+H) $^+$, Cl 37].

Elementary analysis for $\text{C}_{20}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}_3 \cdot \text{HCl} \cdot 0.9\text{H}_2\text{O}$

Calculated: C, 43.70; H, 4.36; Cl, 12.90; N, 10.19; S, 17.50.

Found: C, 43.82; H, 4.49; Cl, 13.27; N, 9.86; S, 17.32.

[0977]

[Example 60]

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

[0978]

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.91 (3H, s), 3.02-3.25 (5H, m), 3.32-3.90 (6H, m), 4.33-4.55 (2H, m), 4.64-4.75 (1H, m), 7.55 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.06 (1H, d, $J=8.8\text{Hz}$), 8.09 (1H, s), 11.42 (1H, br s).

MS (FAB) m/z : 497 $[(M+H)^+, \text{Cl}^{35}]$, 499 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{20}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}_3 \cdot 1.1\text{HCl} \cdot 1.4\text{H}_2\text{O}$

Calculated: C, 42.71; H, 4.46; Cl, 13.24; N, 9.96; S, 17.11.

Found: C, 42.49; H, 4.51; Cl, 13.01; N, 9.76; S, 16.95.

[0979]

[Example 61]

2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine was treated and purified in the same manner as in Example 33, whereby the title compound was obtained.

[0980]

IR(KBr) cm^{-1} : 3016, 1631, 1450, 1432, 1344, 1328, 1276, 1267,

1162, 1135, 998, 727, 578.

¹H-NMR (DMSO-d₆) δ: 3.10-3.23 (4H, m), 3.85 (2H, br s), 4.29 (2H, br s), 4.48 (3H, s), 7.70 (1H, dd, J=8.8, 2.0 Hz), 7.83 (1H, d, J=8.8, 2.0 Hz), 8.17 (1H, d, J=8.8 Hz), 8.23 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.8 Hz), 8.52 (1H, s), 8.71 (1H, d, J=6.8 Hz), 8.98 (1H, d, J=6.8, 2.0 Hz), 9.92 (1H, d, J=2.0 Hz).

MS (FAB) m/z: 487 [M⁺, Cl³⁵], 489 [M⁺, Cl³⁷].

[0981]

[Example 62]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In N,N-dimethylformamide (100 ml), lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxylate (616 mg), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine trifluoroacetate (1.12 g), 1-hydroxybenzotriazole monohydrate (36 mg) and 1-(dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (579 mg) were dissolved and the resulting solution was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Dichloromethane was then added to the residue, followed by washing with water. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The

residue was purified by chromatography on a silica gel column [Φ 3.0 x (1.5 + 8) cm, ethyl acetate : methanol = 100:4], whereby a colorless foam was obtained. The resulting foam was dissolved in 1N HCl (20 ml), followed by concentration under reduced pressure, whereby the title compound (845 mg) was obtained as a pale yellow foam.

[0982]

IR(KBr) cm^{-1} : 3380, 1668, 1623, 1542, 1415, 1342, 1330, 1159, 1135, 1078, 952, 941, 723, 578.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.42-2.80 (5H, m), 2.90 (3H, s), 2.95-3.80 (6H, m), 4.23-4.50 (5/2H, m), 4.60-4.77 (1H, m), 4.98 (1/2H, br s), 5.45-5.55 (1H, m), 6.15 (1/2H, br s), 7.71 (1H, d, $J=8.8\text{Hz}$), 7.78-7.82 (1H, m), 8.07-8.13 (1H, m), 8.15 (1H, d, $J=8.8\text{Hz}$), 8.23 (1H, s), 8.25 (1H, d, $J=8.8\text{Hz}$), 8.49 (1H, s), 11.70-12.00 (1H, m).

MS (FAB) m/z : 548 [$(\text{M}+\text{H})^+$, Cl^{35}], 550 [$(\text{M}+\text{H})^+$, Cl^{37}].

[0983]

In a similar manner to Example 62, the compounds of Examples 63 to 76 were obtained.

[0984]

[Example 63]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[[morpholin-4-yl)carbonyl)methyl]piperazine

Raw materials: lithium 6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[[morpholin-4-yl)carbonyl]methyl]piperazine hydrochloride

[0985]

¹H-NMR (DMSO-d₆) δ: 2.35-2.83 (2H, m), 2.89 (3H, s), 2.95-3.88 (18H, m), 4.31-4.45 (3/2H, m), 4.67 (2H, d, J=15.1 Hz), 5.03 (0.5H, br s), 5.37 (0.5H, d, J=13.7 Hz), 5.79 (1/2H, br s), 7.70 (1H, dd, J=8.8, 2.0 Hz), 7.81 (1H, d, J=8.8 Hz), 8.15 (1H, d, J=8.8 Hz), 8.23 (1H, s), 8.27 (1H, d, J=8.8 Hz), 8.50 (1H, s), 11.50-11.75 (1H, m).

MS (FAB) m/z: 618 [(M+H)⁺, Cl³⁵], 620 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₈H₃₂ClN₅O₅S₂·1.5HCl·3H₂O

Calculated: C, 46.27; H, 5.48; Cl, 12.19; N, 9.63; S, 8.82.

Found: C, 46.49; H, 5.20; Cl, 12.16; N, 9.67; S, 8.88.

[0986]

[Example 64]

N-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]glycine ethyl ester

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, N-[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]glycine ethyl ester trifluoroacetate

¹H-NMR (DMSO-d₆) δ: 1.17-1.24 (3H, m), 2.38 (3H, s), 2.39-2.53 (1H, m), 2.58-2.84 (5H, m), 3.20-3.29 (1H, m), 3.54-

3.81 (4H, m), 3.90-4.00 (1H, m), 4.06-4.17 (1H, m),
 4.32 (1H, d, J=11.7 Hz), 4.47 (1/2H, d, J=13.7 Hz), 5.14 (1/2H, s),
 5.66 (1/2H, d, J=13.7 Hz), 6.42 (1H, br s), 7.68 (1H, d, J=8.3 Hz),
 7.79 (1H, d, J=8.3 Hz), 8.12 (1H, dd, J=8.8, 3.4 Hz), 8.19 (1H, s),
 8.23 (1H, d, J=8.8 Hz), 8.48 (1H, s), 8.52 (1/2H, t, J=5.4 Hz),
 8.61 (1/2H, t, J=5.4 Hz).

MS (FD) m/z: 619 [M⁺, Cl³⁵], 621 [M⁺, Cl³⁷].

Elementary analysis for C₂₇H₃₀ClN₅O₆S₂·0.2HCl·0.1H₂O

Calculated: C, 51.54; H, 4.87; Cl, 6.76; N, 11.13; S, 10.19.

Found: C, 51.31; H, 4.92; Cl, 6.74; N, 10.92; S, 10.01.

[0987]

In the present reaction, the below-described compound
 whose ester bond had been hydrolyzed was obtained.

N-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]piperazin-2-yl]carbonyl]glycine

[0988]

¹H-NMR (DMSO-d₆) δ: 2.37 (3H, s), 2.59-2.83 (6H, m), 3.20-
 3.32 (1H, m), 3.52-3.77 (4H, m), 3.82-3.95 (1H, m), 4.28-
 4.35 (1H, m), 4.45 (1/2H, d, J=13.7 Hz), 5.13 (1/2H, br s),
 5.63 (1/2H, d, J=13.7 Hz), 6.36 (1H, br s), 7.69 (1H, d, J=8.3 Hz),
 7.80 (1H, d, J=8.3 Hz), 8.12 (1H, dd, J=8.8, 3.4 Hz), 8.20 (1H, s),
 8.23 (1H, d, J=8.8 Hz), 8.41 (1/2H, t, J=5.4 Hz), 8.45-8.50 (3/2H, m).

MS (FD) m/z: 592 [(M+H)⁺, Cl³⁵], 594 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₇H₃₀ClN₅O₆S₂·H₂O

Calculated: C, 49.22; H, 4.63; Cl, 5.81; N, 11.48; S, 10.51.

Found: C, 49.11; H, 4.78; Cl, 6.02; N, 11.41; S, 10.25.

[0989]

[Example 65]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-(morpholin-4-yl)carbamoyl]piperazine

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[N-(morpholin-4-yl)carbamoyl]piperazine trifluoroacetate

¹H-NMR (DMSO-d₆ at 100°C) δ: 2.58-2.84 (8H, m), 2.89 (3H, s), 2.98-3.58 (3H, m), 3.40-3.80 (8H, m), 4.10-4.70 (4H, m), 7.65 (1H, dd, J=8.6, 2.4 Hz), 7.79 (1H, dd, J=8.6, 1.2 Hz), 8.09 (1H, d, J=8.6 Hz), 8.14 (1H, s), 8.18 (1H, d, J=8.6 Hz), 8.42 (1H, s), 8.58 (1H, br s).

MS (FAB) m/z: 619 [(M+H)⁺, Cl³⁵], 621 [(M+H)⁺, Cl³⁷].

Elementary analysis for C₂₄H₂₆ClN₄O₅S₂·1.7HCl·1.7H₂O

Calculated: C, 45.56; H, 5.11; Cl, 13.45; N, 10.57; S, 8.93.

Found: C, 45.35; H, 5.34; Cl, 13.46; N, 12.01; S, 8.93.

[0990]

[Example 66]

Ethyl N'-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetate

hydrochloride

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, ethyl N'-[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]hydrazinoacetate hydrochloride

[0991]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.18-1.28 (3H, m), 2.36 (3H, s), 2.65-2.85 (5H, m), 3.23-3.28 (1H, m), 3.31 (2H, s), 3.44-3.75 (4H, m), 4.08-4.24 (3H, m), 4.38 (1/2H, d, $J=13.7\text{Hz}$), 5.01 (1/2H, s), 5.22-5.31 (1H, m), 5.52 (1/2H, d, $J=13.7\text{Hz}$), 6.10 (1/2H, br s), 7.69 (1H, d, $J=8.8, 2.0\text{Hz}$), 7.72-7.80 (1H, m), 7.72-7.80 (3H, m), 8.47 (1H, s), 9.77-9.85 (1H, m).

MS (FAB) m/z : 635 $[(M+H)^+, \text{Cl}^{35}]$, 637 $[(M+H)^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{27}\text{H}_{31}\text{ClN}_6\text{O}_6\text{S}_2 \cdot 1.6\text{HCl} \cdot \text{H}_2\text{O}$

Calculated: C, 45.58; H, 4.90; Cl, 12.95; N, 11.81; S, 9.01.

Found: C, 45.71; H, 5.09; Cl, 12.83; N, 11.46; S, 8.94.

[0992]

[Example 67]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine hydrochloride

Raw materials : lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[N-[[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine hydrochloride

[0993]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.35-2.82 (2H, m), 2.90 (3H, s), 2.95-3.30 (2H, m), 3.32-3.86 (13H, m), 4.05-4.20 (1H, m), 4.23-4.50 (2.5H, m), 4.59-4.70 (1H, m), 5.15 (0.5H, s), 5.50 (0.5H, d, $J=12.2\text{Hz}$), 6.30 (0.5H, s), 7.70 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.80 (1H, d, $J=8.8\text{Hz}$), 8.12-8.38 (4H, m), 8.48 (1H, s), 11.45-11.75 (1H, m).

MS (FAB) m/z : 661 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 663 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

Elementary analysis for $\text{C}_{29}\text{H}_{33}\text{ClN}_6\text{O}_6\text{S}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$

Calculated: C, 48.67; H, 5.07; Cl, 9.91; N, 11.74; S, 8.96.

Found: C, 48.70; H, 5.03; Cl, 10.23; N, 11.55; S, 9.32.

[0994]

[Example 68]

4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]morpholine hydrochloride

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 4-[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]morpholine trifluoroacetate

[0995]

IR (KBr) cm^{-1} : 3396, 2919, 2854, 1652, 1623, 1457, 1112, 954, 723, 578.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.62-2.79 (1H, m), 2.85-3.92 (19H, m), 4.02-

4.13 (1/2H, m), 4.30-4.49 (3/2H, m), 4.58-4.80 (1H, m), 5.24-5.46 (1H, m), 6.28-6.45 (1H, m), 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.83 (1H, d, J=8.8 Hz), 8.12-8.28 (3H, m), 8.53 (1H, s), 11.30-11.80 (1H, m).

MS (FAB) m/z: 604 [(M+H)⁺, Cl³⁵], 606 [(M+H)⁺, Cl³⁷].

[0996]

[Example 69]

4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[ethoxycarbonyl]piperazine

¹H-NMR (CDCl₃) δ: 1.25-1.35 (3H, m), 2.43-2.94 (9H, m), 3.31 (1/2H, dt, J=12.7, 3.4 Hz), 3.60-3.76 (2.5H, m), 3.83 (1/2H, d, J=11.7 Hz), 3.89 (1/2H, d, J=11.7 Hz), 4.19-4.30 (2H, m), 4.42-4.50 (1H, m), 4.55 (1/2H, 14.2 Hz), 5.76 (1/2H, 14.2 Hz), 7.57 (1H, dd, J=8.3, 1.5 Hz), 7.77 (1H, dd, J=8.3, 1.5 Hz), 7.89-7.94 (3H, m), 8.34 (1H, s).

MS (FAB) m/z: 563 [(M+H)⁺, Cl³⁵], 565 [(M+H)⁺, Cl³⁷].

[0997]

[Example 70]

Methyl 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetate

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[methoxycarbonylmethyl]piperazine

[0998]

IR(KBr) cm^{-1} : 2944, 2846, 2788, 1735, 1619, 1455, 1164.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.40-2.92 (10H, m), 3.04 (1H, dd, $J=16.1, 8.8\text{Hz}$), 3.16-3.27 (1/2H, m), 3.42-3.55 (1/2H, m), 3.60-3.72 (5H, m), 3.83-3.97 (2H, m), 4.60 (1/2H, d, $J=13.2\text{Hz}$), 5.21 (1/2H, br s), 5.70 (1/2H, d, $J=13.2\text{Hz}$), 6.15 (1/2H, br s), 7.57 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.75 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.87-7.95 (3H, m), 8.30 (1H, s).

MS (FAB) m/z : 563 [$(\text{M}+\text{H})^+$, Cl^{35}], 565 [$(\text{M}+\text{H})^+$, Cl^{37}].

[0999]

[Example 71]

2-[[N-(tert-butoxy)amino]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[(N-tert-butoxy)carbonyl]piperazine trifluoroacetate

[1000]

IR(KBr) cm^{-1} : 2979, 1675, 1465, 1199, 1184, 1166, 1135, 721.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.15-1.25 (9H, m), 2.36 (3H, s), 2.37-

2.49 (1H, m), 2.67-2.84 (5H, m), 3.25-3.35 (1H, m), 3.59-3.78 (3H, m), 4.13-4.25 (1H, m), 4.38 (1H, d, J=13.2 Hz), 5.01 (1/2H, br s), 5.52 (1/2H, d, J=13.2 Hz), 5.14 (1/2H, s), 6.21 (1/2H, br s), 7.69 (1H, dd, J=8.8, 2.0 Hz), 7.76-7.74 (1H, m), 8.14 (1H, d, J=8.8 Hz), 8.21 (1H, s), 8.24 (1H, d, J=8.8 Hz), 8.47-8.53 (1H, m), 10.75-10.78 (1H, m).

MS (FAB) m/z: 606 [(M+H)⁺, Cl³⁵], 608 [(M+H)⁺, Cl³⁷].

[1001]

[Example 72]

[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetamide hydrochloride

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[carbamoylmethyl]piperazine hydrochloride

IR (KBr) cm⁻¹: 1671, 1616, 1465, 1457, 1419, 1332, 1162, 1133, 1124, 1078, 956, 701, 578.

[1002]

¹H-NMR (DMSO-d₆) δ: 2.30-2.80 (4H, m), 2.90 (3H, s), 2.93-3.25 (2H, m), 3.30-3.55 (1H, m), 3.62-3.88 (3H, m), 4.05-4.43 (2.5H, m), 4.60-4.71 (1H, m), 5.05 (0.5H, br s), 5.34 (0.5H, d, J=13.2 Hz), 5.69-5.84 (0.5H, m), 6.82 (0.5H, br s), 6.93 (0.5H, br s), 7.37-7.50 (1H, m), 7.70 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=8.8 Hz), 8.10-8.29 (3H, m), 8.49 (1H, s).

MS (FAB) m/z : 576 $[(M+H)^+, Cl^{35}]$, 578 $[(M+H)^+, Cl^{37}]$.

[1003]

[Example 73]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-isopropyl)carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[(N-isopropyl)carbamoyl]piperazine hydrochloride

[1004]

IR(KBr) cm^{-1} : 2967, 2933, 1666, 1625, 1542, 1463, 1344, 1332, 1159, 1135, 954, 725, 578.

1H -NMR (DMSO- d_6) δ : 1.00-1.10(6H,m), 2.50-2.80(2H,m), 2.91(3H,s), 2.93-3.50(4H,m), 3.60-3.79(2H,m), 3.82-3.95(1H,m), 4.18-4.30(1H,m), 4.32-4.50(1.5H,m), 4.60-4.77(1H,m), 4.97(0.5H,s), 5.03(0.5H,d,J=13.2Hz), 5.90(0.5H,s), 7.70(1H,d,J=8.8Hz), 7.79(1H,d,J=8.8Hz), 7.92-8.00(1H,m), 8.22H8.22(1H,d,J=8.8Hz), 8.18-8.28(2H,m), 8.48(1H,s).

MS (FAB) m/z : 576 $[(M+H)^+, Cl^{35}]$, 578 $[(M+H)^+, Cl^{37}]$.

[1005]

[Example 74]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[piperidin-1-

yl)carbonyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[[piperidin-1-yl)carbonyl)methyl]piperazine hydrochloride

[1006]

IR(KBr)cm⁻¹: 2931, 2854, 1623, 1455, 1334, 1159, 1135, 1124, 1078, 954, 700, 578.

¹H-NMR (DMSO-d₆) δ: 1.20-1.70(8H,m), 2.35-2.82(2H,m), 2.90(3H,s), 2.95-3.88(11H,m), 4.31-4.45(1.5H,m), 4.62-4.76(1H,m), 5.03(0.5H,br s), 5.34(0.5H,d,J=13.2Hz), 5.70(0.5H,br s), 7.70(1H,d,J=8.8Hz), 7.81(1H,d,J=8.8Hz), 8.15(1H,d,J=8.8Hz), 8.22(1H,s), 8.27(1H,d,J=8.8Hz), 8.50(1H,s).

MS (FAB) m/z: 616 [(M+H)⁺, Cl³⁵], 618 [(M+H)⁺, Cl³⁷].

[1007]

[Example 75]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[[N-(2-

methoxybenzyl)]carbamoyl]piperazine hydrochloride

[1008]

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.42-3.54 (9H,m), 3.62-3.85 (5H,m), 4.12-4.50 (3.5H,m), 4.60-4.77 (1H,m), 5.09 (1/2H,br s), 5.43-5.52 (1/2H,m), 6.11-6.19 (1/2H,m), 6.85-7.00 (2H,m), 7.16-7.29 (2H,m), 7.72 (1H,d, $J=10.7\text{Hz}$), 7.80-7.86 (1H,m), 8.16 (1H,d, $J=8.8\text{Hz}$), 8.22-8.28 (2H,m), 8.50 (1H,s), 8.65-8.72 (1H,m).

MS (FAB) m/z : 654 $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$, 656 $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$.

[1009]

[Example 76]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

Raw materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)]carbamoyl]piperazine

[1010]

IR(KBr) cm^{-1} : 2931, 1544, 1463, 1423, 1344, 1332, 1157, 1133, 1078, 954, 943, 723, 578.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.42-2.82 (2H,m), 2.92 (3H,s), 2.95-3.79 (13H,m), 4.21-4.80 (3.5H,m), 5.02 (1/2H,br s), 5.47 (1/2H,d, $J=12.2\text{Hz}$), 6.07 (1/2H,br s),

7.70 (1H, dd, J=8.8, 2.0 Hz), 7.79 (1H, d, J=8.8 Hz),
 8.13 (1H, d, J=8.8 Hz), 8.17-8.32 (3H, m), 8.48 (1H, s), 11.09-
 11.40 (1H, m).

MS (FAB) m/z: 592 [(M+H)⁺, Cl³⁵], 594 [(M+H)⁺, Cl³⁷].

[1011]

[Example 77]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

In tetrahydrofuran (10 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine (2.08 g) was dissolved, followed by the addition of ethanol (20 ml) and a 1N aqueous solution (3.70 ml) of sodium hydroxide. The resulting mixture was stirred at room temperature for 1 hour. After concentration of the reaction mixture under reduced pressure, the residue was added with water (20 ml). The precipitate thus formed was collected by filtration, whereby the title compound (1.39 g) was obtained as a pale yellow foam.

[1012]

IR (KBr) cm⁻¹: 1731, 1625, 1461, 1346, 1332, 1315, 1159, 1135, 1078, 954, 943, 723, 580.

¹H-NMR (DMSO-d₆) δ: 2.32-3.86 (11H, m), 4.27 (1H, d, J=11.7 Hz), 4.35-4.48 (3/2H, m), 4.59-4.78 (1H, m), 5.21 (1/2H, m), 5.38-5.52 (1/2H, m), 6.34-6.47 (1/2H, m), 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.83 (1H, d, J=8.8 Hz), 8.16 (1H, d, J=8.8 Hz), 8.23 (1H, s),

8.27 (1H, d, J=8.8Hz), 8.53 (1H, s), 11.60-11.90 (1H, m).

Elementary analysis for $C_{23}H_{23}ClN_4O_5S_2 \cdot 1.3HCl \cdot 1.5H_2O$

Calculated: C, 45.33; H, 4.51; Cl, 13.38; N, 9.19; S, 10.52.

Found: C, 45.69; H, 4.55; Cl, 13.29; N, 9.21; S, 10.21.

[1013]

[Example 78]

N'-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetate

In the same manner as in the previous Example, the title compound was obtained using ethyl N'-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetate hydrochloride as a raw material.

[1014]

MS (FAB) m/z: 607 [(M+H)⁺, Cl³⁵], 609 [(M+H)⁺, Cl³⁷].

¹H-NMR (DMSO-d₆ at 100°C) δ: 2.41 (3H, s), 2.65-3.30 (6H, m),

3.37-3.77 (8H, m), 4.16 (1H, d, J=12.7Hz),

7.64 (1H, dd, J=8.7, 2.4Hz), 7.78 (1H, dd, J=8.7, 1.6Hz),

8.07 (1H, d, J=8.7Hz), 8.11 (1H, d, J=1.6Hz), 8.16 (1H, d, J=8.7Hz),

8.42 (1H, s).

Elementary analysis for $C_{25}H_{27}ClN_6O_6S_2 \cdot 2H_2O$

Calculated: C, 46.69; H, 4.86; N, 13.07; S, 9.97.

Found: C, 46.87; H, 4.86; N, 12.82; S, 9.62.

[1015]

[Example 79]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[N-(tetrahydropyran-2-yloxy)]carbamoyl]piperazine

In N,N-dimethylformamide (20 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid (141 mg), 2-tetrahydropyranyloxyamine (180 mg), 1-hydroxybenzotriazole monohydrate (11 mg), 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (145 mg) and potassium carbonate (129 mg) were dissolved, followed by stirring overnight at room temperature. The reaction mixture was concentrated under reduced pressure.

Dichloromethane was added to the residue, followed by washing with water. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (Φ 0.7 x 25.0 cm, dichloromethane : methanol = 100:3), whereby the title compound (308 mg) was obtained as a colorless foam.

[1016]

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50-1.89 (6H, m), 2.45-2.55 (3H, m), 2.72-3.00 (6H, m), 3.57-3.97 (5H, m), 4.28 (0.5H, d, $J=12.2\text{Hz}$), 4.35 (0.5H, d, $J=12.2\text{Hz}$), 4.52-4.61 (0.5H, m), 4.92 (0.5H, s), 5.02 (0.5H, br s), 5.06-5.10 (0.5H, m), 5.55-5.65 (0.5H, m), 5.88 (0.5H, br s), 6.21 (0.5H, br s), 7.51-7.58 (1H, m), 7.77-

7.93 (4H, m), 8.35 (1H, s), 9.61 (0.5H, br s), 10.10 (1H, br s).

MS (FAB) m/z: 634 [(M+H)⁺, Cl³⁵], 636 [(M+H)⁺, Cl³⁷].

[1017]

[Example 80]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-hydroxamic acid

In methanol (10 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[N-(tetrahydropyran-2-yloxy)]carbamoyl]piperazine (297 mg) was dissolved, followed by the addition of 1N hydrochloric acid (10 ml). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was purified by "HP-20" (Φ 1.7 x 20.0 cm, acetonitrile : water = 1:5), whereby the title compound (65 mg) was obtained as a pale yellow foam.

[1018]

¹H-NMR (CDCl₃) δ: 2.32-2.73 (2H, m), 2.91 (3H, s), 2.97-3.30 (3H, m), 3.35-3.50 (1H, m), 3.63-3.76 (2H, m), 4.22-4.48 (2.5H, m), 4.61-4.75 (1H, m), 4.99 (0.5H, s), 5.47 (0.5H, d, J=12.2Hz), 6.24 (0.5H, s), 7.70 (1H, d, J=8.8Hz), 7.75-7.85 (1H, m), 8.15 (1H, d, J=8.8Hz), 8.23 (1H, s), 8.25 (1H, d, J=8.8Hz), 8.48 (1H, s), 10.26 (1H, br s), 10.97 (1H, br s).

MS (FAB) m/z: 550 [(M+H)⁺, Cl³⁵], 552 [(M+H)⁺, Cl³⁷].

[1019]

[Example 81]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-hydroxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In dichloromethane (10 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (195 mg) was dissolved, followed by the dropwise addition of a tribromoborane - dichloromethane solution (1.0M, 2.08 ml) at -78°C. The reaction mixture was heated to room temperature and stirred overnight. To the reaction mixture, methanol (2 ml), sodium carbonate (200 mg) and water (3 ml) were added to extract the organic layer, followed by drying over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The solid thus precipitated was collected by filtration while being washed with 1N hydrochloric acid, whereby the title compound (50 mg, 24%) was obtained as a pale yellow solid.

[1020]

¹H-NMR (DMSO-d₆) δ: 2.36-2.87 (9H,m), 3.11-3.28 (1H,m), 3.59-3.80 (3H,m), 4.12-4.45 (3.5H,m), 4.48-4.57 (1/2H,m), 5.08 (1/2H,br s), 6.19 (1/2H,br s), 6.63-6.81 (2H,m), 6.98-7.15 (2H,m), 7.70 (1H,dd,J=8.3,1.5Hz), 7.78-7.84 (1H,m), 8.13 (1H,d,J=8.8Hz), 8.20-8.28 (2H,m), 8.49 (1H,s), 8.50-8.62 (1H,m), 9.45 (1/2H,s), 9.50 (1/2H,s).

MS (FAB) m/z : 640 $[(M+H)^+, Cl^{35}]$, 642 $[(M+H)^+, Cl^{37}]$.

[1021]

[Example 82]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine

To a solution of 6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (58.1 mg) in tetrahydrofuran (3.2 ml), *n*-butyllithium (a 1.59N hexane solution, 320 ml) was added at -78°C , followed by stirring for 1 hour and then stirring at 0°C for 30 minutes. The reaction mixture was cooled to -78°C and a carbon dioxide gas was introduced thereinto for 1 hour. After the reaction mixture was heated to room temperature over 30 minutes, it was concentrated. To a solution of the resulting residue in *N,N*-dimethylformamide (6.0 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (177 mg, 510 μmol) was dissolved, followed by the addition of 1-(dimethylaminopropyl)-3-ethylcarbodiimide (98.0 mg, 511 μmol) and 1-hydroxybenzotriazole (69.0 mg, 511 μmol) at room temperature and then, diisopropylethylamine (185 ml, 1.06 mmol) at 0°C . After stirring overnight at room temperature, the reaction mixture was added with methylene chloride (20 ml) and a saturated aqueous solution (50 ml) of sodium bicarbonate and the organic layer was collected. The resulting organic layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, washed with water (50 ml), dried over anhydrous sodium sulfate and concentrated under reduced

pressure. The residue thus obtained was purified twice by preparative thin-layer chromatography on a silica gel (methylene chloride : acetone : methanol = 10:5:1). The white solid thus obtained was dissolved in a 1N ethanol hydrochloride solution and the resulting solution was concentrated. After the addition of water, the mixture was concentrated again, whereby the title compound (74.7 mg) was obtained as a white solid.

[1022]

IR(KBr)cm⁻¹: 3396, 2918, 2850, 2538, 1620, 1456, 1432, 1344, 1329, 1282, 1161, 955, 941, 729.

¹H-NMR (DMSO-d₆) δ: 2.68(1H, br d, J=15.1Hz), 2.78-2.92(1H, br), 2.85(3H, s), 3.04(4H, br s), 3.26(1H, br s), 3.52(1H, br s), 3.72(4H, br s), 4.20(1H, br d, J=15.1Hz), 4.43(1H, br d, J=15.1Hz), 6.92(1H, s), 7.71(1H, dd, J=2.0, 8.8Hz), 7.80(1H, d, J=8.8Hz), 8.15(1H, d, J=8.8Hz), 8.23(1H, s), 8.25(1H, d, J=8.8Hz), 8.48(1H, s), 11.64(1H, br s).

MS (FAB) m/z: 474 [(M+H)⁺].

Elementary analysis for C₂₃H₂₄ClN₃O₄S·1.1HCl·1.7H₂O

Calculated: C, 50.72; H, 5.27; N, 7.71; Cl, 13.67; S, 5.89.

Found: C, 50.58; H, 5.39; N, 7.69; Cl, 13.94; S, 5.85.

[1023]

[Example 83]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine

To 6-(t-butoxycarbonyl)-2-[[4-(chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine (1.28 g, 2.24 mmol), a saturated ethanol hydrochloride solution (50 ml) was added at room temperature. The resulting mixture was stirred for 20 minutes, followed by concentration, whereby the title compound (1.26 g) was obtained as a white solid.

[1024]

IR(KBr) cm^{-1} : 3396, 2924, 2615, 2544, 1957, 1655, 1610, 1473, 1454, 1425, 1448, 1336, 1286, 1157, 941, 731, 580.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.02 (2H, br t, $J=5.3\text{Hz}$), 3.05 (2H, t, $J=6.4\text{Hz}$), 3.42-3.49 (2H, brm), 3.52 (2H, br t, $J=5.3\text{Hz}$), 3.75 (2H, br t, $J=5.3\text{Hz}$), 4.33 (2H, br t, $J=5.3\text{Hz}$), 7.56 (1H, br d, $J=8.3\text{Hz}$), 7.89 (1H, d, $J=8.3\text{Hz}$), 7.89 (1H, dd, $J=1.5, 8.8\text{Hz}$), 7.98 (1H, dd, $J=2.0, 8.8\text{Hz}$), 8.34 (1H, d, $J=8.8\text{Hz}$), 8.43 (1H, s), 8.44 (1H, d, $J=8.8\text{Hz}$), 8.67 (1H, br s), 9.87 (2H, br s).

MS (FAB) m/z : 471 [$(\text{M}+\text{H})^+$, Cl^{35}].

Elementary analysis for $\text{C}_{23}\text{H}_{23}\text{ClN}_4\text{O}_3\text{S}\cdot 1.9\text{HCl}\cdot 0.9\text{H}_2\text{O}$

Calculated: C, 49.64; H, 4.84; Cl, 10.07; N, 18.48; S, 5.76.

Found: C, 49.64; H, 4.96; Cl, 10.01; N, 18.73; S, 5.93.

[1025]

[Example 84]

2-[[4-(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine

To a solution of 2-[[4-(chloronaphthalen-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine (174 mg) in methylene chloride (3.5 ml), triethylamine (95.6 ml), acetic acid (58.9 ml), formaldehyde (a 37% aqueous solution, 42.0 ml) and sodium triacetoxymethylborohydride (110 mg) were added at room temperature, followed by stirring for 15 minutes. To the reaction mixture, a saturated aqueous solution (10 ml) of sodium bicarbonate and methylene chloride (10 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on a silica gel (methylene chloride : methanol = 15:1). The white solid thus obtained was dissolved in a 1N ethanol hydrochloride solution, followed by concentration, whereby the title compound (170 mg) was obtained as a white solid.

[1026]

IR(KBr) cm^{-1} : 3359, 2918, 2544, 1655, 1641, 1475, 1431, 1342, 1331, 1284, 1155, 953, 941, 727, 579.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.04 (3H, d, $J=3.9\text{Hz}$), 3.17 (2H, br s), 3.26 (2H, br s), 3.38-3.65 (2H, m), 3.68 (2H, br s), 3.39 (2H, br s), 4.40-4.70 (2H, m), 4.57 (2H, br s), 7.57 (1H, d, $J=7.8\text{Hz}$), 7.84-7.92 (2H, m), 7.98 (1H, d, $J=8.8\text{Hz}$), 8.33 (1H, d, $J=8.3\text{Hz}$), 8.42 (1H, s), 8.43 (1H, d, $J=8.8\text{Hz}$), 8.67 (1H, s), 11.86 (1H, br s).

MS (FAB) m/z : 485 [$(\text{M}+\text{H})^+$, Cl^{35}].

[1027]

[Example 85]

2-[[4-(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

A saturated ethanol hydrochloride solution (25 ml) was added to 1,5-bis(t-butoxycarbonyl)-2-[[4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (300 mg) at room temperature, followed by stirring for 1 hour. The reaction mixture was concentrated and water was added to the concentrate. The resulting mixture was concentrated under reduced pressure. To the residue, a saturated methanol hydrochloride solution (25 ml) was added at room temperature, followed by stirring for 1 hour. After concentration of the reaction mixture, water was added and the resulting mixture was concentrated under reduced pressure, whereby the title compound (200 mg) was obtained as a white solid.

[1028]

IR(KBr) cm^{-1} : 3290, 2918, 2762, 2559, 1614, 1483, 1454, 1381, 1340, 1323, 1244, 1155, 1147, 1136, 978, 955, 727, 575.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.77 (2H, br t, $J=5.9\text{Hz}$), 3.03 (4H, t, $J=5.3\text{Hz}$), 3.30 (2H, br t, $J=5.9\text{Hz}$), 3.73 (4H, br t, $J=5.3\text{Hz}$), 3.99 (2H, br s), 6.32 (1H, d, $J=2.0\text{Hz}$), 7.73 (1H, dd, $J=2.0, 8.8\text{Hz}$), 7.83 (1H, dd, $J=2.0, 8.8\text{Hz}$), 8.17 (1H, d, $J=8.8\text{Hz}$), 8.25 (1H, d, $J=2.0\text{Hz}$), 8.28 (1H, d, $J=8.8\text{Hz}$), 8.50 (1H, br s), 9.07 (2H, br), 11.38 (1H, br).

MS (FAB) m/z : 459 $[(M+H)^+, Cl^{35}]$.

Elementary analysis for $C_{22}H_{23}ClN_4O_3S \cdot 1.1HCl \cdot 0.3H_2O$

Calculated: C, 52.38; H, 4.94; N, 11.11; Cl, 14.76; S, 6.36.

Found: C, 52.48; H, 4.92; N, 11.07; Cl, 14.48; S, 6.65.

[1029]

[Example 86]

2-[[4-(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

In methylene chloride (4.5 ml), 2-[[4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (200 mg) was suspended, followed by the addition of triethylamine (125 ml), acetic acid (77.0 ml), formaldehyde (a 37% aqueous solution, 56.1 ml) and sodium triacetoxyborohydride (139 mg) at room temperature. The resulting mixture was stirred for 15 minutes. To the reaction mixture, a saturated aqueous solution (20 ml) of sodium bicarbonate and methylene chloride (10 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (25 g of silica gel, methylene chloride : methanol = 10:1 → 7:1). The resulting white solid was dissolved in a 1N ethanol hydrochloride solution. After concentration of the resulting

solution, water was added to the concentrate and the mixture was concentrated again, whereby the title compound (133 mg) was obtained as a white solid.

[1030]

IR(KBr) cm^{-1} : 3213, 2918, 2650, 2530, 1604, 1585, 1508, 1491, 1456, 1342, 1331, 1157, 727, 579.

^1H -NMR (DMSO- d_6) δ : 2.72-2.86 (1H, m), 2.83 (3H, d, $J=4.9\text{Hz}$), 2.87-2.99 (1H, m), 3.03 (4H, br t, $J=4.4\text{Hz}$), 3.19-3.31 (1H, m), 3.46-3.64 (1H, m), 3.74 (4H, br t, $J=4.4\text{Hz}$), 3.97 (1H, dd, $J=7.8, 14.2\text{Hz}$), 4.20 (1H, br d, $J=14.2\text{Hz}$), 6.32 (1H, d, $J=2.4\text{Hz}$), 7.72 (1H, dd, $J=2.4, 8.8\text{Hz}$), 7.82 (1H, dd, $J=2.0, 8.8\text{Hz}$), 8.16 (1H, d, $J=8.8\text{Hz}$), 8.25 (1H, d, $J=2.0\text{Hz}$), 8.27 (1H, d, $J=8.8\text{Hz}$), 8.51 (1H, br s), 10.84 (1H, br s), 11.42 (1H, br s).

MS (FAB) m/z : 473 [$(\text{M}+\text{H})^+$, Cl^{35}].

Elementary analysis for $\text{C}_{23}\text{H}_{25}\text{ClN}_4\text{O}_3\text{S}\cdot 1.3\text{HCl}\cdot 0.7\text{H}_2\text{O}$

Calculated: C, 51.83; H, 5.24; N, 10.51; Cl, 15.30; S, 6.02.

Found: C, 51.83; H, 5.37; N, 10.30; Cl, 15.35; S, 6.09.

[1031]

[Example 87]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

In methylene chloride (3.0 ml), 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-

4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (149 mg) was suspended, followed by the addition of methanol (0.6 ml), triethylamine (82.5 ml), acetic acid (51.0 ml, 891 mmol), acetaldehyde (19.5 ml) and sodium triacetoxyborohydride (74.0 mg) at room temperature. The resulting mixture was stirred for 15 minutes. To the reaction mixture, a saturated aqueous solution (30 ml) of sodium bicarbonate and methylene chloride (15 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (30 g of silica gel, methylene chloride : methanol = 10:1). The resulting white solid was dissolved in a 1N ethanol hydrochloride solution (10 ml). After concentration of the resulting solution, water (30 ml) was added to the concentrate and the mixture was concentrated again, whereby the title compound (81.7 mg) was obtained as a white solid.

[1032]

IR(KBr) cm^{-1} : 3386, 3226, 2918, 2586, 1603, 1585, 1491, 1454, 1427, 1344, 1331, 1163, 1136, 1078, 933, 727, 579.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.26(3H, t, $J=7.3\text{Hz}$), 2.72-2.82(1H, m), 2.86-3.00(1H, m), 3.02(4H, br s), 3.12-3.64(6H, m), 3.73(4H, br s), 3.96(1H, dd, $J=7.8, 14.1\text{Hz}$), 4.22(1H, br d, $J=14.1\text{Hz}$), 6.31(1H, d, $J=2.4\text{Hz}$), 7.71(1H, br d, $J=8.8\text{Hz}$), 7.81(1H, br

d, J=8.8Hz), 8.16(1H, d, J=8.8Hz), 8.23(1H, br s),
8.26(1H, d, J=8.8Hz), 8.50(1H, br s), 10.39(1H, br s), 11.40(1H, br
s).

MS (FAB) m/z: 486 [(M+H)⁺, Cl³⁵].

Elementary analysis for C₂₄H₂₇ClN₄O₃S·1.2HCl·2.0H₂O

Calculated: C, 50.86; H, 5.73; N, 9.88; Cl, 13.76; S, 5.66.

Found: C, 51.11; H, 5.71; N, 9.58; Cl, 13.60; S, 5.66.

[1033]

[Example 88]

5-(t-Butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

In methylene chloride (15 ml), 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (780 mg) was suspended, followed by the addition of a saturated aqueous solution (15 ml) of sodium bicarbonate and di-t-butyl dicarbonate (506 ml) at room temperature. The resulting mixture was stirred for 1 hour. To the reaction mixture, water (30 ml) and methylene chloride (30 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 20 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (75 g of silica gel, methylene chloride : acetone = 8:1 → 2:1). The resulting white

solid was dissolved in a 1N ethanol hydrochloride solution. After concentration of the resulting solution, water was added to the concentrate and the mixture was concentrated again, whereby the title compound (641 mg) was obtained as a white solid.

[1034]

¹H-NMR (CDCl₃) δ: 1.46(9H, s), 2.61(2H, br s), 3.12(4H, br t, J=4.9Hz), 3.66(2H, br s), 3.90(4H, br t, J=4.9Hz), 4.36(2H, br s), 6.19(1H, d, J=2.0Hz), 7.57(1H, dd, J=1.7, 9.0Hz), 7.76(1H, br d, J=8.8Hz), 7.86-7.97(3H, m), 8.29(1H, br s), 9.24(1H, br s).

[1035]

[Example 89]

5-(t-Butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 5-(t-butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (33.0 mg) in N,N-dimethylformamide (15 ml), sodium hydride (60% in oil, 3.5 mg) was added at 0°C. After stirring for 10 minutes, methyl iodide (4.5 ml) was added and the resulting mixture was stirred for 1 hour at a temperature maintained at 0°C. To the reaction mixture, a saturated aqueous solution (10 ml) of ammonium chloride, methylene chloride (20 ml) and water (30 ml) were added to cause separation. The resulting water layer was extracted with methylene chloride (10 ml). The organic layers were

combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on a silica gel (methylene chloride : acetone = 9:1), whereby the title compound (32.3 mg) was obtained as a colorless, transparent viscous substance.

[1036]

¹H-NMR (CDCl₃) δ: 1.46(9H, s), 2.58(2H, br s), 3.12(4H, br t, J=4.5Hz), 3.50(3H, s), 3.68(2H, br s), 3.84(4H, br t, J=4.5Hz), 4.32(2H, br s), 6.02(1H, s), 7.58(1H, dd, J=2.0, 8.8Hz), 7.77(1H, dd, J=1.7, 8.5Hz), 7.88-7.97(3H, m), 8.32(1H, br s).

[1037]

[Example 90]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To 5-(t-butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (280 mg), a saturated ethanol hydrochloride solution (25 ml) was added at room temperature, followed by stirring for 1 hour. The reaction mixture was then concentrated. Water (10 ml) was added to the concentrate, followed by concentration under reduced pressure, whereby the title compound (210 mg) was obtained as a white solid.

[1038]

IR (KBr) cm^{-1} : 3381, 2918, 2748, 1622, 1583, 1495, 1454, 1342, 1331, 1248, 1163, 1136, 953, 935, 879, 726, 579, 476.

^1H -NMR (DMSO- d_6) δ : 2.81 (2H, br t, $J=5.6\text{Hz}$), 3.05 (4H, br s), 3.35 (2H, br t, $J=5.6\text{Hz}$), 3.42 (3H, s), 3.69 (4H, br s), 3.97 (2H, br s), 6.18 (1H, s), 7.73 (1H, dd, $J=2.0, 8.8\text{Hz}$), 7.83 (1H, dd, $J=2.0, 8.8\text{Hz}$), 8.18 (1H, d, $J=8.8\text{Hz}$), 8.27 (1H, br s), 8.28 (1H, d, $J=8.8\text{Hz}$), 8.50 (1H, br s), 9.34 (1H, br d, $J=27.4\text{Hz}$).

MS (FAB) m/z : 473 $[(M+H)^+, \text{Cl}^{35}]$.

Elementary analysis for $\text{C}_{23}\text{H}_{25}\text{ClN}_4\text{O}_3\text{S} \cdot 1.4\text{HCl} \cdot 1.2\text{H}_2\text{O}$

Calculated: C, 50.63; H, 5.32; N, 10.27; Cl, 15.59; S, 5.88.

Found: C, 50.71; H, 5.53; N, 10.14; Cl, 15.53; S, 5.90.

[1039]

[Example 91]

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

In methylene chloride (10 ml), 2-[[4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (170 mg) was suspended, followed by the addition of methanol (10 ml), triethylamine (100 ml), acetic acid (62.0 ml), formaldehyde (a 37% aqueous solution, 46.5 ml) and sodium triacetoxyborohydride (115 mg) at room temperature. The resulting mixture was stirred for 30 minutes. To the reaction

mixture, a saturated aqueous solution (50 ml) of sodium bicarbonate and methylene chloride (30 ml) were added to separate the water layer. The water layer thus obtained was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (30 g of silica gel, methylene chloride : methanol = 10:1 \rightarrow 7:1). The resulting white solid was dissolved in a 1N ethanol hydrochloride solution. After the concentration of the resulting solution, water was added to the concentrate and the resulting mixture was concentrated again, whereby the title compound (162 mg) was obtained as a white solid.

[1040]

IR(KBr) cm^{-1} : 3396, 2924, 2663, 2586, 1622, 1581, 1456, 1342, 1329, 1248, 1163, 1136, 955, 937, 727, 579.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.77-3.00 (5H, m), 3.06 (4H, br s), 3.23-3.37 (1H, m), 3.43 (3H, s), 3.55-3.65 (1H, m), 3.69 (4H, br s), 3.90-4.03 (1H, m), 3.93 (3H, s), 4.19 (1H, br d, $J=11.7\text{Hz}$), 6.18 (1H, s), 7.74 (1H, dd, $J=2.0, 8.8\text{Hz}$), 7.83 (1H, dd, $J=2.0, 8.8\text{Hz}$), 8.18 (1H, d, $J=8.8\text{Hz}$), 8.27 (1H, br s), 8.28 (1H, d, $J=8.8\text{Hz}$), 8.51 (1H, br s), 11.00 (1H, br s).

MS (FAB) m/z : 487 [$(\text{M}+\text{H})^+$, Cl^{35}].

Elementary analysis for $\text{C}_{24}\text{H}_{27}\text{ClN}_4\text{O}_3\text{S}\cdot 1.4\text{HCl}\cdot 1.4\text{H}_2\text{O}$

Calculated: C, 51.18; H, 5.58; N, 9.95; Cl, 15.11; S, 5.69.

Found: C, 51.09; H, 5.83; N, 9.78; Cl, 15.37; S, 5.79.

[1041]

[Test 1] Measurement of FXa inhibitory action (IC_{50})

In a 96-well microtiter plate, 10 μ l of a sample solution, 40 μ l of a 100 mM tris · 200mM sodium chloride · 0.2% BSA (pH: 7.4) buffer and 10 μ l of 0.05 U/ml human FXa ("Cosmobio-ERL HFXa-1011", dissolved in and diluted with a measuring buffer) were poured in portions, followed by the addition of 40 μ l of 750 μ M S2222 (product of Chromogenix). An increase (mOD/min) in the absorbance at 405 nm was measured at room temperature. From the below-described equation, an inhibitory ratio % of each sample was determined. On a logarithmic probability paper, the final concentration of the sample and inhibitory ratio % were plotted along the abscissa and the ordinate, respectively, whereby a 50% inhibitory concentration (IC_{50}) was determined.

[1042]

Inhibitory ratio (%) = $(1 - \text{OD of sample} \div \text{OD of control}) \times 100$

[1043]

(Results) The compounds of Examples 32, 54, 61 and 63 exhibited Fxa 50% inhibitory concentrations of 20 nM, 5.0 nM, 30 nM and 12.5 nM, respectively.

[1044]

[Test 2] Measurement of thrombin inhibitory action (IC_{50})

In a 96-well microtiter plate, 10 μ l of a sample solution, 40 μ l of a 100 mM tris · 200mM sodium chloride · 0.2% BSA (pH: 7.4) buffer and 10 μ l of 4 U/ml human thrombin (Sigma Chemical,

dissolved in and diluted with a measuring buffer) were poured in portions, followed by the addition of 40 μ l of 500 μ M S2266 (product of Chromogenix). An increase (mOD/min) in the absorbance at 405 nm was measured at room temperature. From the below-described equation, an inhibitory ratio % of each sample was determined. On a logarithmic probability paper, the final concentration of the sample and inhibitory ratio % were plotted along the abscissa and the ordinate, respectively, whereby a 50% inhibitory concentration (IC_{50}) was found.

[1045]

Inhibitory ratio (%) = $(1 - OD \text{ of sample} \div OD \text{ of control}) \times 100$

[1046]

(Results) The compound of Example 54 exhibited a thrombin 50% inhibitory concentration of 1.05 μ M.

[1047]

[Test 3] Measurement of coagulation extending action
(measurement of prothrombin time)

Plasma (20 μ l) and 20 μ l of a sample solution were mixed. To the resulting mixture, 40 ml of cynplastin (product of Organon Teknika) was added and the coagulation time was measured. The concentration of the sample (CT2) at which the coagulation time of the plasma was increased twice was found and it was designated as an index of anticoagulant action.

(Results) The compound of Example 33 showed CT2 of 0.35 μ M.

[1048]

[Test 4] Ant-FXa activity in blood and prothrombin time extending action

1) Method

A sample was dissolved or suspended in a 0.5% (w/v) methyl cellulose solution and the resulting solution or suspension was orally administered (10 ml/kg) to a 8 to 11 week-old rat (Wistar male rat (Nippon SLC Co., Ltd.)) which had been fasted overnight. After administration of the sample, the blood to which 1/10 part by weight of 3.13% (w/v) sodium citrate had been added was collected from the cervical vein under anesthesia with halothane. The rat was awakened except during the blood collection. Feeding was re-started 6 hours after the blood collection. From each blood sample, the plasma was separated by centrifugal separation and anti-FXa activity in the blood and prothrombin time extending action were measured.

[1049]

2) Measuring method

2-1) Measurement of anti-FXa activity in the plasma

In a 96-well plate, 5 μ l of the plasma was poured in portions, followed by the addition of 55 μ l of a 8:1:2 mixture of 100 mM tris \cdot 200 mM sodium chloride \cdot 0.2% BSA (pH 7.4) buffer, water and 0.1 U/ml human Factor Xa solution (dissolved in and diluted with a measuring buffer) and 40 μ l of 750 μ M S-2222. After stirring for 10 seconds in a plate mixer, an increase (mOD/min) of the absorbance at 405 nm was measured at room temperature. The inhibitory ratio was calculated as follows:

[1050]

An inhibitory ratio (%) = (1 - OD of sample ÷ OD of control on average relative to blood-collecting time of sample) x 100

[1051]

2-2) Measurement of coagulation extending action in oral administration (measurement of prothrombin time)

To 20 µl of the plasma, 40 µl of cynplastin (Organon Teknika/USA) was added and the coagulation time was measured. The ratio of the prothrombin time after the administration of the sample relative to the prothrombin time before the administration of the sample was designated as an index of the coagulation extending action.

[1052]

3) Results

The compound of Example 36 showed an anti-FXa activity of 68% in the plasma one hour after the oral administration of 30 mg/kg of the sample. It extended the prothrombin time.

[1053]

[Test 5] Test of anti-thrombus effects in a tissue thromboplastin-derived rat DIC model

A rat was anesthetized with halothane. After the collection of the blood (for measurement of the number of platelets, anti-FXa activity and TAT) from its cervical vein by using 1/10 part by weight of 3.13% (w/v) sodium citrate, the sample was administered orally. At an appropriate time after the administration, the rat was intraperitoneally anesthetized

(1 mg/kg) with Nembutal (50 mg/ml pentobarbital sodium, Abbott Laboratories), followed by intravenous drip of 0.2 U/ml of tissue thromboplastin (Thromboplastin C plus, Dade Diagnostics of P. R. Inc.,) from the femoral vein for one minute at a rate of 2.5 to 3.0 ml/kg/min. The blood was collected (for measuring the number of platelets and anti-FXa activity) from the cervical vein 10 minutes after the intravenous drip and 20 minutes after that, the blood was collected (for measuring TAT) from the cervical vein. The number of platelets, anti-FXa activity in the plasma and TAT concentration of each blood sample were measured. The number of the platelets was measured by an automatic cytometer, while the anti-FXa activity in the plasma was measured in a similar manner to that described in Test 4.

[1054]

For the measurement of TAT (Thrombin-anti Thrombin = complex), EnzygnostR TAT micro kit (Boering Verke) was employed.

[1055]

As a result of the oral administration of 30 mg/kg of the compound of Example 36, apparent anti-FXa action in the plasma was recognized and a decrease in the number of the platelets and an increase in the TAT concentration were suppressed (the tissue thromboplastin was administered one hour after the administration of the sample).

[Document Name] ABSTRACT

[Abstract]

[Problem] To provide, as an excellent anticoagulant, a novel sulfonyl derivative or salt thereof, or solvate thereof which has strong FXa inhibitory action, exhibits prompt, sufficient and long-lasting anti-thrombus effects even by the oral administration and has reduced side effects.

[Means for the Solution] A sulfonyl derivative represented by the following formula (I):

[Chemical formula 1]



[wherein, Q^1 represents a saturated or unsaturated dicyclic fused ring group which may have a substituent or a saturated or unsaturated tricyclic fused ring group which may have a substituent,

Q^2 represents a single bond, an oxygen atom, a sulfur atom, a linear or branched C_{1-6} alkylene group, etc.,

Q^A represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a substituent, etc. and

T^1 represents a carbonyl group, etc., or salt thereof, or solvate thereof.

[Selected Figure of Drawings] None

10-227449

【Document Name】 Data of Correction ex officio
【Corrected Document】 Patent for Application

〈Recognized Information/Additional Information〉

【Applicant】 PETITIONER
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10-227449

PERSONAL HISTORY OF APPLICANT

Identification Number [000002831]

1. Date of change August 28, 1990
[Reason of change] New Registration
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